EXHIBIT C20

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION ***THIS DOCUMENT RELATES TO ALL CASES***	**MDL NO. 16-2738 (FLW) (LHG)**

EXPERT REPORT OF IE-MING SHIH, MD, PHD FOR GENERAL CAUSATION *DAUBERT* HEARING

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EXPERT REPORT ON THE ALLEGED CAUSAL ROLE OF TALC IN OVARIAN CANCER

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INTRODUCTION, SCOPE OF REPORT, AND SUMMARY OF OPINIONS

I understand that plaintiffs' experts – in particular, Dr. Ghassan Saed and Dr. Sarah Kane – have offered opinions for litigation regarding the biological mechanisms by which perineal talc might cause or worsen the prognosis of ovarian cancer. I was asked to review these litigation opinions and to assess their scientific validity and the reliability of the methods employed to formulate them. Based on my experience and expertise as a pathologist who focuses on gynecological pathology and carcinogenesis, I have formed the following opinions, which I detail in this report:

1. Dr. Saed's and Dr. Kane's opinions related to the biological plausibility of the theory that talc powder use can cause ovarian cancer or increase the risk of ovarian cancer are not the product of reliable methods and are contrary to established scientific knowledge.

2. Dr. Saed's experimental results, including those published (in press), are fraught with research design flaws, and the results fail to support or negate his hypothesis – they are simply irrelevant. He has not developed any evidence that supports the theory that talc powder has a carcinogenic role in ovarian cancer development.

3. Based on the recent research findings as published, I did not find any evidence – molecular, biological, pathological or epidemiological in nature – that supports the conclusion that talc can cause or increase the risk of ovarian cancer.

4. Dr. Saed failed to provide an adequate disclosure of a significant conflict of interest in his manuscript, and his failure to do so calls all of his work and conclusions into question.

SUMMARY OF RELEVANT EXPERIENCE AND QUALIFICATIONS

I am a pathologist with expertise in gynecologic pathology, especially in the carcinogenesis and etiology of ovarian cancer (i.e., how ovarian cancer develops in women). I am certified in Anatomic Pathology by the American Board of Pathology. I received my medical degree from the Taipei Medical University in 1988, as well as a Ph.D. in Biomedical Graduate Study (Pathology) from the University of Pennsylvania in 1993. Thereafter, I completed a residency in Anatomic Pathology and a clinical fellowship in Gynecologic Pathology at the Johns Hopkins Hospital, and a research fellowship in Cancer Genetics at Johns Hopkins Oncology Center.

I currently hold an appointment as the Richard W. TeLinde Distinguished Professor of Gynecologic Pathology in the Department of Gynecology and Obstetrics at Johns Hopkins Medical Institutions (see the link below), where I also hold secondary appointments in the Departments of Oncology and Pathology. I additionally serve as the Director of the Johns Hopkins Inter-departmental TeLinde Gynecologic Pathology Research Program (www.gynecologycancer.org) and as a Co-director of the Breast and Ovarian Cancer Program at the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins University School of Medicine. Of note, the Richard W. TeLinde distinguished (endowed) professorship is considered the most prestigious position of gynecologic pathology in the country. https://professorships.jhu.edu/professorship/richard-w-telinde-distinguished-professorship-in-gynecological-pathology/.

My research focuses on exploring carcinogenesis, genomic landscapes and pathogenesis of ovarian and endometrial cancers, developing new target-based therapy and applying innovative technology for early detection of gynecologic cancer. My research team has proposed the new model in classifying ovarian cancer, which has become widely used, helped elucidate the origin of ovarian cancer and develops new technology to detect ovarian cancer. My research group also pioneered elucidating the molecular landscapes in different types of ovarian cancer and identifying novel genes and pathways involved in cancer initiation, chromatin remodeling, chromosomal instability, cytokinesis and tumor invasion in ovarian cancer, providing new insight into how ovarian cancer occurs.

I have received many research awards from US government agencies, including the National Institutes of Health ("NIH") and National Cancer Institute ("NCI") and the Department of Defense (DoD), to study ovarian cancer-related topics. Pursuant to these awards, my research team, in collaboration with medical and gynecologic oncologists, is initiating new clinical trials that capitalize on our new molecular research findings. For example, I am the Principal Investigator in the recent NIH/NCI awarded SPORE (Specialized Program of Research Excellence) for Ovarian Cancer ($12.5 million for 5 years, 2018-2023), and I am leading the multi-institutional team for translational ovarian cancer research, including the development of early detection and novel therapies by further understanding ovarian cancer initiation and progression and by better understanding ovarian cancer biology. I have also been the Principal Investigator or key project leader in several research projects supported by NIH/NCI, DoD and several private foundation awards. Under my leadership, the TeLinde Gynecologic Pathology Research Program has generated more than $6.6 million of research funds each year, making my research program the most successful gynecologic pathology research group in the country.

I have published more than 350 original articles and book chapters in prestigious medical and science journals such as *New England Journal of Medicine*, *Cancer Cell*, *Journal of National Cancer Institute*, *PNAS*, *Science*, *Lancet Oncology*, *Nature* and *Nature Medicine*, etc., which have been cited more than 32,000 times in the literature, making me one of the most cited gynecologic pathologists in the world. My 2017 paper published in *New England Journal of Medicine* (related to molecular changes in the very beginning of a specific type of ovarian cancer) received the Most Influential Paper Prize in Gynecology field in 2017 from the Columbia Hospital for Women Research Foundation. I am also one of the contributors to book chapters in gynecology textbooks and the WHO Classification of Tumors of Female Reproductive Organs

published by the IARC 2014 in defining different types of ovarian cancer. I have been invited to give more than 110 lectures worldwide, many of which related to ovarian cancer. In particular, I have given 36 invited lectures on the carcinogenesis of ovarian (high-grade) cancer. These lectures reflect my academic status and international reputation on the subject of how ovarian cancer develops. I have been on several advisory boards, such as the NCI Ovarian Task Force of Gynecologic Cancer Steering Committee and Ovarian Cancer Research Alliance, and served as an editorial board member of *Cancer Research*, *Journal of Pathology*, *American Journal of Pathology* and several others.

I am serving as an expert on ovarian cancer carcinogenesis in this litigation. In particular, I was asked to review the expert report and related work of Dr. Ghassan Saed. My reimbursement rate is commensurate to my experience and academic status mentioned above: $800/hr for preparing reports, $1400/hr for deposition, $1200/case for reviewing tissue materials and generating pathology reports.

OPINIONS

The following opinions are based on my expertise, experience, training, my previous and ongoing research, as well as knowledge from reading the relevant scientific literature. Based on an assessment of the totality of the evidence, and following the methodology set forth below, I hold the opinions offered in this report to a reasonable degree of scientific and medical certainty. I reserve the right to amend or supplement this report as new information becomes available.

This report is divided into four sections. I begin with a brief overview (section A). I then express my opinions in two parts. Section B sets forth the serious problems with Dr. Saed's research findings provided in his expert report and the in-press article. I conclude that Dr. Saed's research does not support the conclusions he offers in his expert report or his article. Section C addresses my understanding of whether talc powder is a cause of ovarian cancer, including the lack of scientific evidence to support the conclusion that talc could cause ovarian cancer. And Section D discusses the problematic implications of Dr. Saed's failure to disclose in his manuscript that the funding he received was from a law firm with a vested interest in the results of his study.

A. Overview

Very few true ovarian cancer risks have been established. They include the BRCA1/2 inherited mutations and the increased accumulated times of ovulation in a woman's lifetime (affected by oral contraceptive use, oocyte induction, child bearing, breast feeding, etc.). Approximately 1.3% of women in the general population will develop ovarian cancer sometime during their lives (Howlader et al., 2017). But in women who carry the germline mutations, the chance dramatically increases by the age of 80 to ~ 44% of women who inherit a harmful BRCA1 mutation and ~ 17% of women who inherit a harmful BRCA2 mutation (Kuchenbaecker et al., 2017). Ovarian cancer precursor lesions are also enriched in BRCA1/2 mutation carriers (Visvanathan et al., 2018). Similarly, more ovulations increase the risk of ovarian cancer, the so-called "incessant ovulation theory" of ovarian cancer (Fathalla, 2013; Havrilesky et al., 2013; Lurie et al., 2008). The above conclusions are reproducible and unequivocal and have become generally accepted in the field of ovarian cancer carcinogenesis.

Several studies have reported an association between ovarian cancer and the use of talcum powder on the perineal area. In 2010, the International Agency for Research on Cancer ("IARC") classified perineal use of talc as a possible carcinogen. As compared to the published reports confirming scientifically accepted ovarian cancer risks, the studies focusing on delineating the alleged ovarian cancer-promoting roles of talc are fraught with several issues, including study design, incorrect interpretation of the study results, and premature conclusions. Therefore, credible support for the theory that talc can cause ovarian cancer is lacking. In Section C of this report, I will carefully examine the published evidence (especially after 2010) that is related to the alleged role of talc in the development of ovarian cancer.

B. Dr. Saed's And Dr. Kane's Conclusions

In this part, I identify problems related to the interpretations and conclusions made by Dr. Saed, who conducted experiments on talc powder and argues that talc could cause ovarian cancer development, as well as the opinions of Dr. Kane, who puts forth a number of the same points raised by Dr. Saed but also offers a few additional opinions of her own. I first address Dr. Saed's opinions (B.1) and in-press article (B.2). I then address the additional opinions offered by Dr. Kane (B.3).

1. Dr. Saed's statements in his expert report

Dr. Saed purports to have conducted laboratory research that supports the theory that talc use can cause ovarian cancer. According to Dr. Saed:

"1. Johnson's Baby Powder elicits an inflammatory response in normal ovarian and tubal cells and in ovarian cancer cells that can result in the development and progression of ovarian cancer." (*See, e.g.*, Saed Rep. at 20; *see also id.* at 10.)
"2. This pro-carcinogenic process involves oxidative stress, alteration of the redox environment by increasing oxidant enzymes and decreasing anti-oxidant enzymes, promotion of cell proliferation, inhibition of apoptosis, and induction of specific genetic mutations." (*See, e.g.*, Saed Rep. at 20; *see also id.* at 16-17.)
"3. Johnson's Baby Powder exposure results in elevation of CA-125, a clinically relevant biomarker for ovarian cancer, in normal and ovarian cancer cells." (*See, e.g.*, Saed Rep. at 20; *see also id.* at 18.)
"4. The molecular effects resulting from Johnson's Baby Powder exposure exhibit a clear dose-response pattern." (*See, e.g.*, Saed Rep. at 20; *see also id.* at 17.)

Dr. Saed concludes that "Johnson's Baby Powder exposure can cause ovarian cancer." (*See, e.g.*, Saed Rep. at 20.)

Dr. Saed's research is unreliable and his conclusions reveal a fundamental misunderstanding of ovarian cancer, for several reasons.

Excessive Talc Concentration. The talc concentrations used in Dr. Saed's experiments (from 20-100 mg/ml) are higher than would be encountered in real-world (i.e., physiological) conditions. If use of such a high concentration was deemed appropriate by the researcher, he

needed to show a similar talc concentration range in human gynecologic tissues from those who had prior exposures. Otherwise, his data cannot be extrapolated to patients in real life. But no such showing was made here. Therefore, the observations made in Dr. Saed's report concerning cell growth, inhibition of cell death (apoptosis) and CAT expression and enzymatic activity in epithelial ovarian cancer cell lines and other cell lines (which are not relevant to ovarian cancer initiation) – are most likely the results of abnormally high concentrations of talc, which is not relevant to human biology.

Use of Cancer Cell Lines. Dr. Saed's study is also problematic because, although he was attempting to support the hypothesis that talc powder can cause ovarian cancer, Dr. Saed's study relies extensively on claimed effects of talc powder (under a non-physiological concentration) on cancer cell lines. Cancer cell lines were originally derived from cancer tissues and they are already cancer cells, meaning not normal cells anymore. If one wishes to show that the chemical of interest is potentially carcinogenic, one should show its biological effects on normal non-transformed cells – in this case, the normal fallopian tube epithelial cells. But this was not reported in Dr. Saed's study. (Dr. Saed did include immortalized cancer-free cells as well, but these are not normal cells.) Therefore, the research team missed the point regarding whether talc particles can cause ovarian cancer. Another problem with the study design is that the researchers mistakenly used an A2780 cell line as an ovarian high-grade serous cancer cell line. But in fact, A2780 is unlikely an ovarian high-grade serous cancer line and should not have been relevant in this study, reflecting the limited knowledge of the research group in studying ovarian cancer (Anglesio et al., 2013; Domcke et al., 2013).

Another related concern is the experiment related to oxidative stress. According to Dr. Saed, there is "*substantial evidence demonstrating that altered oxidative stress may play a role in maintaining the oncogenic phenotype of [epithelial ovarian cancer] cells.*" (*See, e.g.*, Saed Rep. at 17-18 (emphasis added).) But again, Dr. Saed's research does not show whether this is true in normal fallopian tube epithelial cells that give rise to ovarian cancer. In fact, what Dr. Saed really showed is the effect on cancer cells, which are characterized by a very different molecular and biological landscape from normal counterparts. If one wishes to demonstrate whether the chemical can induce malignant changes, one should focus on studying the effects of the chemical on normal fallopian tube epithelial cells.

Irrelevance of CA-125 Finding. Dr. Saed misstates the relevance of his findings with respect to CA-125. CA-125 is an FDA-approved ovarian cancer biomarker for monitoring disease status after treatment. It is definitely not a cancer-specific biomarker, as many normal tissues express CA-125 in the absence of cancer or its precursor. Therefore, CA-125 should not be considered as indicating the onset or heightened risk of the development of ovarian cancer. Thus, Dr. Saed's statement in the conclusion of his report that CA-125 is a "clinically relevant biomarker for ovarian cancer" (*see, e.g.*, Saed Rep. at 20) is misleading, and the data from CA-125 are not relevant to support the researcher's conclusion.

Extrapolation From In Vivo Experiment. Dr. Saed claims in his summary paragraph that "*This study has shown a dose-dependent significant increase in key pro-oxidants . . . and a concomitant decrease in key antioxidant enzymes . . . in all talc treated cells (both normal and ovarian cancer) compared to their controls.*" (*See, e.g.*, Saed Rep. at 19.) But the significance of

this finding is unclear. Although a dose-dependent phenomenon is relevant to assessing causal effect in biological studies, a broader conclusion on causation would depend on demonstration of a similar dose-dependent effect in women – i.e., that women who apply talc perineally have a higher risk when they are exposed to a higher dosage of talc powder (more frequent use and/or longer period of time, for example). Dr. Saed's experiment obviously does not answer this question. Moreover, all the data as presented in Dr. Saed's report were based on *in vitro* (in petri dishes or test tubes) experiments, and their significance to *in vivo* (in real animal or human tissues) is essentially unknown. Therefore, Dr. Saed's leap to a causal conclusion in his "Summary of Opinions" is not supported from the perspective of careful scientific investigation.

Studies Not Conducted. Dr. Saed acknowledged that there are other studies that he could have conducted – and even proposed conducting – but chose not to conduct due to claimed limitations on time and money. For example, he testified that animal experiments would be necessary to confirm that his *in vitro* experiments actually modeled chronic inflammation (Saed Dep. vol. 2, 542:16-25), but he did not conduct animal studies because he did not "have the time to do it and the money" (Saed Dep. vol. 1, 50:10-13). Dr. Saed similarly explained that he ultimately decided not to conduct other tests he had initially proposed, including one that he deemed essential to establishing a "cause and effect" relationship between talc exposure and ovarian cancer, because such testing would have taken more time and money. (Saed Dep. vol. 2, 498:6-17, 501:14-502:5, 503:10-505:20, 509:23-510:9, 513:9-14.) But science is a purely evidence-based and evidence-driven discipline, and limitations of money and time (or other matters mentioned in Dr. Saed's deposition, including reagents and assays) cannot excuse a lack of scientific rigor.

2. Dr. Saed's "In-Press" Paper in *Reproductive Science*

There are several problems with Dr. Saed's article as well, most of which are similar to the problems I have already identified with respect to his expert report.

Cell Lines. Three "ovarian cancer" cell lines were used in Dr. Saed's research. SKOV3 and A2780 in this new publication are not true ovarian high-grade serous cancer cells (Anglesio et al., 2013; Domcke et al., 2013). The third cell line employed, TOV112D, is a known ovarian endometrioid carcinoma cell line (Anglesio et al., 2013). This is concerning because none of the three "ovarian" cancer cell lines used were derived from high-grade serous carcinoma, which is the most common histological subtype of ovarian cancer and the disease focus of several of plaintiffs' epidemiology experts in this litigation.

Concentration. The talcum powder in this study was dissolved in DMSO at a concentration of 500 mg in 10 ml. (Manuscript at 5.) It is certainly unknown whether this concentration is relevant to ovarian tissue exposure to perineal use of talcum powder in women. Therefore, the significance of the results – including the expression levels of antioxidant enzymes, SOD, CAT, GPX and GSR as well as pro-oxidants, INOS, NO_2-/NO_3- and MPO in normal and ovarian cancer cells – is unclear.

Purported Mutations. The Saed paper states that, "*[r]emarkably, talc exposure induced specific point mutations that are known to alter the activity in some of these key enzymes.*" (Manuscript at 2.) The gene variants that were reported by Saed were not listed as cancer driver genes

(Tamborero, 2013), and therefore their biological significance in initiating human ovarian cancer is totally unknown. There is no evidence demonstrating these variants occur significantly in human ovarian cancer either. In addition, this statement has no solid support from the data provided (Table 2). Single nucleotide polymorphisms (SNPs) – a type of genetic variation – did occur in certain enzymes in some cell lines, but the reported mutant allele frequency (MAF) was low in general. This discrepancy is significant. A fundamental tenet of cancer genetics is that the mutations that drive tumor development, such as *TP53*, *KRAS* and many others, should be much higher (> 50% in cancer cell lines and > 10% in cancer tissues because of contamination from normal tumor stromal cells). As an example, *KRAS* mutation is an established cancer driver event, and it usually mutates in one of a pair of alleles (inherited from either mother or father) but not in the other, so the MAF is 50%. Thus, the reported findings suggest that mutations likely occur as a random event. In fact, the authors also said in the Result section that, "*[i]ntriguingly, talc treatment reversed this SNP genotype to the normal genotype (Table 2)*." (Manuscript at 8.) Based on my expertise in biology and cancer genetics, I can attest that this result of genotyping is of unknown significance and in any event is not related to the risk of talcum powder in promoting ovarian cancer. This is because these changes will not significantly affect any functions of the enzyme (meaning that the mutations do not have carcinogenic potential) unless the biochemistry can provide further evidence to support a different finding. In short, showing SNP changes does not prove or even suggest that an exposure is carcinogenic. The investigator would need to show a malignant or pre-cancerous change in tissue – and Dr. Saed has not done this.

CA-125. The authors state that talc treatment increased CA-125 levels in normal and ovarian cancer cells. (Manuscript at 8.) But for the reasons explained above, this is of no biological significance at all. CA-125 (also known as mucin 16) is a "biomarker" to monitor ovarian cancer during treatment. It has nothing to do with the disease biology (development of ovarian cancer). Nor, in any event, is CA-125 specific to ovarian cancer or, indeed, cancer generally. In gynecologic pathology, women who have several benign diseases (not cancers) have an increased CA-125 level in serum. Gynecologic tissues such as normal fallopian tube epithelium express CA-125. The best interpretation is that the increased CA-125 levels reflect a cell response to environmental stress (talc powder) – and not that this response has anything to do with ovarian cancer.

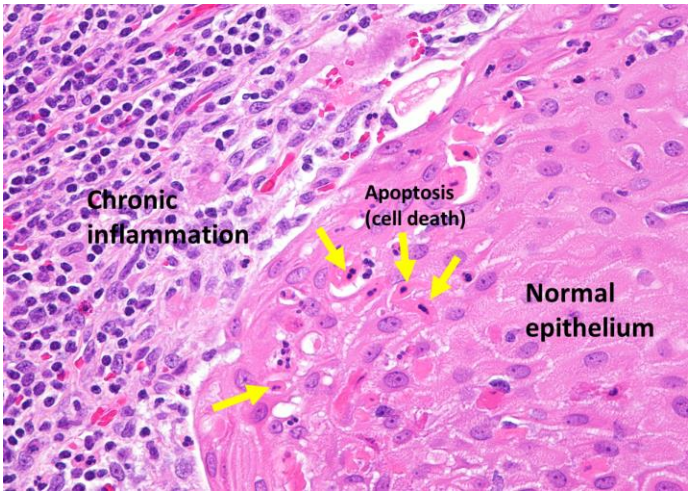

Figure 1. A representative photomicrograph showing the cell death (apoptosis) of epithelial cells in response to inflammation. There are many cells undergoing apoptosis (a kind of cell death) (arrows). These cells are characterized by pyknotic nuclei and eosinophilic condensed cytoplasm. Surrounding the epithelial nest are abundant lymphocytes and some leukocytes.

Cell Proliferation. The final conclusion provided in this paper is that the talc treatment increased cellular proliferation and decreased apoptosis (cell death). (Manuscript at 8.) But cell proliferation is not specific to cancer, as normal cells also proliferate all the time (like bone marrow blood cells and uterine epithelial cells) to replace normally aging cells. Thus, increased cellular proliferation itself does not suggest carcinogenicity. In other words, cellular proliferation is required but not sufficient to induce cancer. Rather, conceptually, if talc were a carcinogen, it would damage cell DNA first (mutagenic), causing either (1) growth arrest in non-transformed "normal" epithelial cells that repair DNA damage; or (2) cell death when the DNA damage is extensive and beyond the repair capacity of cells (**Figure 1**). But the result published is just the opposite (i.e., increased cell growth), and thus does not support the conclusion that talc is a mutagen or carcinogen. There are also numerous flaws associated with this experiment. For example, a time dependent cellular proliferation and apoptosis should be shown, different talc concentrations should be tested, more rigorous cell growth assays should be used, and more "normal" tubal epithelial and ovarian surface epithelial cells including the freshly prepared (non-transformed) ones should be used.

The assay for apoptosis suffered a similar pitfall in that other apoptotic markers should be employed. Moreover, reduced apoptosis itself is not a marker for tumorigenesis. In fact, apoptosis is more frequently seen in ovarian cancer precursor lesions and ovarian cancer than in normal counterparts (fallopian tube epithelium). And in any event, whether this talc-induced increased proliferation and decreased apoptosis can be observed in vivo is not known. Therefore, these *in vitro* results and conclusions cannot be extrapolated to support the hypothesis that talc use can cause ovarian cancer.

3. Dr. Kane's Opinions

Dr. Kane has also expressed an opinion on the alleged causal role of talc in ovarian cancer development. Dr. Kane's opinions are mostly similar to those described by Dr. Saed, and these opinions are covered by the points I have set forth above (in B.1 and B.2). But Dr. Kane also offers two additional opinions: (1) that "*[t]here is also evidence that these [talcum powder] products can be transported through the lymphatic system (Cramer 2007)"* or by *"inhalation leading to lymphatic transport to the ovaries (Suzuki 1991, Marchiori 2010, Frank 2011)*"; and (2) that "*[t]here are chemical similarities between asbestos and talc and there are striking pathological similarities between invasive serous ovarian cancer and mesothelioma.*" (*See, e.g.*, Kane Rep. at 4-5.) I explain the invalidity of these arguments as support for the hypothesis that talc powder is causally related to ovarian cancer risk in this section.

"Lymphatic transport." Although the lymphatic transportation of inhaled topically applied talc powder could occur in rare cases, this is not relevant to the central argument that talc is carcinogenic in the ovary. If talc particles can travel through the lymphatic channel to the ovaries, they should be able to reach other human body parts and tissues as well because the lymphatic system runs throughout the body. There are no reports showing that talc is associated with other types of female (or male) cancer like colon cancer, liver cancer, stomach cancer, prostate cancer and pancreatic cancer (where lymphatic circulation is active), just to name a few. In addition, notwithstanding Dr. Kane's suggestion that talc powder may be inhaled into the lungs as a pathway to the lymphatic system, the American Cancer Society has stated that no

increased risk of lung cancer has been reported with the use of cosmetic talcum powder, which can be inhaled during topical use in women. (*See* American Cancer Society official site: https://www.cancer.org/cancer/cancer-causes/talcum-powder-and-cancer.html.) Finally, even if talc may be present in lymphatics and lymph nodes either through skin and mucosa or by inhalation, the evidence that this mechanism can cause ovarian cancer is entirely lacking because no experimental results have demonstrated that the talc in the lymphatic vessels in fallopian tubes is present close to the ovarian cancer precursors in the fallopian tube, the origin of high-grade serous ovarian cancer. In addition, if they are carcinogenic, their presence in the lymph nodes (where the lymphatic drainage occurs) should lead to cancer in the lymph nodes (i.e., lymphoma), and there is no evidence of such a relationship.

"Chemical similarities between asbestos and talc" This is incorrect. First, talc is not asbestos. Structural similarity of chemical compounds does not mean they have the same functions or effects. For example, benzene is a well-known carcinogen that induces leukemia when a person is repeatedly over-exposed. As a result, benzene is being replaced by its many related chemical derivative compounds, like phenol and aniline. These benzene derivatives are structurally similar to benzene but they, unlike benzene, are not classified as carcinogens. Another example is estradiol, which is the most active estrogen and a known carcinogen for reproductive organ cancers in women. By contrast, both estrone and estriol are closely related to estrogen and bear structural resemblance to estradiol, but by themselves are not considered to be carcinogens. Therefore, although both talc and asbestos have structural similarity to some degree, talc is not asbestos. Second, morphological features of ovarian high-grade serous carcinoma and mesothelioma are strikingly different from the view of a board-certified pathologist, and their distinct histological features serve as the foundation for pathologists to distinguish both diseases and render correct diagnoses in the pathology reports without difficulty (although historically, prior to more advanced pathological understanding, advanced peritoneal mesothelioma may have been misdiagnosed as ovarian cancer). I have encountered numerous ovarian serous carcinomas and can attest that they bear no similarity to mesotheliomas in histopathology. Moreover, both diseases have different etiology and molecular features in their development. Therefore, Dr. Kane's statement is totally irrelevant and reveals a misunderstanding of gynecological pathology.

C. The lack of sufficient evidence to support talc as a cause of ovarian cancer

In this part, I set forth my expert opinion on whether there is any cogent evidence showing that talc powder can cause ovarian cancer. As I explain, such evidence is lacking.

According to Merriam-Webster's dictionary and the dictionary of NCI, a carcinogen is a substance that causes cancer. As an example, coal ash deposits have heavy concentrations of hexavalent chromium, which is a carcinogen. Carcinogens cause cancer due to their ability to damage the genome and induce cancer-driver (but not passenger) mutations that promote cancer development (Martincorena, 2017). Thus, in order to prove that any substance is carcinogenic, it is not sufficient to demonstrate exposure. One must also demonstrate that the exposure can cause biological effects and tissue/cellular changes (like precursor lesions).

As I noted above, perineal use of cosmetic talcum powder has been classified as "possibly carcinogenic to humans" by IARC (Group 2b). It should be emphasized that the term "possibly" implies uncertainty at the time when the statement was originally made by the IARC in 2010.

And further analyses of the data (including publications after 2010) have further called into question the possible carcinogenicity of talc.

The debate over whether talcum particles can cause ovarian cancer is longstanding. But despite several decades of research, the science does not support such a conclusion. Moreover, data from several studies are not correctly interpreted because of "confirmation bias" – i.e., a preference for data or conclusions that confirm rather than negate the hypothesis that talc and ovarian cancer are related. Dr. Saed's experimental result is an example of this phenomenon.

When an unbiased review is exercised on the data that have been published in this topic, one quickly realizes that there is essentially no cogent evidence to support the suggestion that talc acts as a carcinogen in the female genital tract, including the ovary. Proof of the carcinogenic role of any agent (either biological, physical or chemical) is not a trivial undertaking; indeed, it requires robust study designs and ample samples with overwhelming consensus from the researchers in that particular field.

One example of such a robust undertaking to prove carcinogenicity involves cervical cancer, which is caused by human papilloma virus (HPV). In this case, cervical cancers and their precursors contain HPV in the epithelial cells, can be prevented by avoiding exposure to HPV or by effective immunization (HPV vaccine), are molecularly characterized by oncogenic activation by HPV particles, and can be induced by HPV oncoproteins in animal models (Roden and Wu, 2006; Roden and Stern, 2018; Sasagawa et al., 1992). This finding that HPV causes cervical cancer was awarded with the 2008 Nobel Prize of Physiology and Medicine www.nobelprize.org/prizes/medicine/2008/press-release/). By contrast, the evidence to support the causal role of talc in ovarian cancer is conflicting, ambiguous and completely lacking from the perspective of rigorous scientific approaches. The differences in these lines of evidence are briefly summarized in **Table 1** and elaborated below.

Table 1. Comparison of HPV and perineal talc use as carcinogens in women.

Features	**HPV causes cervical cancer**	**Talc causes ovarian cancer**
Relative risk association	Almost all are HPV associated	Equivocal; some show ~ 1.3
Present in cancer precursor lesions	Yes	No evidence of tissue reaction
Animal model(s) to support	Well established	No evidence
Molecular mechanisms	Well characterized	Not credible; with concerns

1. The new paradigm of ovarian cancer genesis – that ovarian serous carcinomas originate not in ovarian tissues, but rather in the precursor lesions in the fallopian tubes – has been widely accepted (Kurman and Shih Ie, 2011, 2016; Kurman and Shih, 2010; Wu et al., 2018) (**Figure 2**). To claim that talc can cause ovarian cancer, one needs to not only demonstrate that talc has been deposited in the fallopian tissues,[1] but also that talc powder depositions are associated with tissue reaction, such as foreign body giant cell reaction, granulation tissues and chronic inflammation – and that those reactions then cause cancer. Talc may be inert to fallopian tube tissues, and its

[1] To confirm the presence of talc, birefringent materials would need to be identified in tissue, and those materials would need to be confirmed as talc using biochemistry or biophysical approaches.

presence should not be construed as biologically significant or related to the induction of any inflammatory response unless proven otherwise.

2. It has been established that mutations of TP53, a tumor suppressor gene, are the first molecular genetic alteration in initiating ovarian serous carcinoma in humans and such mutations are present in almost all ovarian high-grade serous carcinomas (Kuhn et al., 2012; Vang et al., 2016; Vang et al., 2013; Wu et al., 2018). TP53 mutation is also required to develop ovarian cancer in mouse models. In several published research papers, including our own (Kobayashi et al., 2015; Perets et al., 2013), inactivation of TP53 or p53 abnormality can cause ovarian cancer in mouse models. If one would like to establish the causal relationship between talc exposure and the risk of ovarian cancer, it is essential to demonstrate that talc exposures leads to TP53 mutations or inactivation. However, there is no evidence that talc exposure is associated with TP53 mutations or p53 abnormality in normal fallopian tube epithelium where ovarian cancer precursors arise. Without this direct molecular pathology evidence, a causal relationship of talc and ovarian cancer cannot be established (see below).

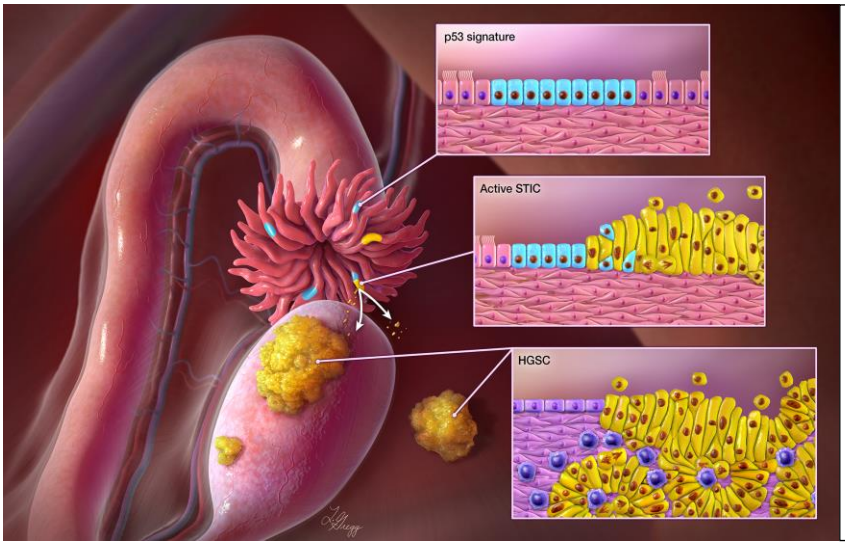

Figure 2. Schematic representation of the current paradigm of ovarian carcinogenesis. Fallopian tube is the source of ovarian (high-grade) serous carcinoma precursors, including p53 signature, serous tubal intraepithelial carcinoma (STIC). Ovarian cancer (but not its precursors) is usually accompanied by abundant inflammatory cells (blue cells in the inset).

3. Recent advancements in genetic sequencing technology have made it possible to observe the specific changes to DNA caused by identified mutagens – and even to "tease apart the superimposed effects of several mutational exposures and processes to determine which ones occurred during the development of individual tumors" (Poon et al., 2014). Therefore, the mutation signature serves as cogent evidence that a potential carcinogen causes a certain type of human cancer. But there is a lack of such evidence showing that talc-induced/caused ovarian serous carcinomas are characterized by mutation signatures unique to those associated with talc exposures.

4. A number of epidemiological studies clearly fail to show an association between talc exposure and women who develop ovarian cancer, including prospective cohort studies (Houghton et al., 2014; Gertig et al., 2000; Gates et al. 2010; Gonzalez et al. 2016). The association between talc use in the perineal region and ovarian cancer was investigated in the Nurses' Health Study, published by Gertig (Gertig et al., 2000) and in a follow-up study by Gates (Gates et al. 2010). "In this cohort study, arguably the strongest type of study because of its partly prospective

ascertainment of exposure, there was no association between cosmetic talc use and risk of all subtypes of ovarian cancer combined" (Langseth et al., 2007).

In another, more recent, prospective cohort study by Gonzalez et al., the authors reported that there was little association between baseline perineal talc use and subsequent ovarian cancer (HR: 0.73, CI: 0.44, 1.2). In this report, douching was more common among talc users (odds ratio: 2.1, CI: 2.0, 2.3), and douching at baseline was associated with increased subsequent risk of ovarian cancer (HR: 1.8, CI: 1.2, 2.8). The authors concluded that douching but not talc use was associated with increased risk of ovarian cancer in this study, known as the Sister Study (Gonzalez et al., 2016). In another important study reported by Nicole Urban et al., based on 74,786 Women's Health Initiative (WHI) Observational Study (OS) participants, the authors concluded that "CA125 and HE4 contributed significantly to a risk prediction classifier combining serum markers with epidemiologic risk factors. The hybrid risk classifier may be useful to identify post-menopausal women who would benefit from timely surgical intervention to prevent ovarian cancer" (Urban et al., 2015). However, talc use is not a risk factor in both univariate and multivariate analyses (*Id.*).

In some population-based case-control studies, investigators reported a weak association between reported perineal talc exposure and ovarian cancer. The "risk association" reported in those studies should not be construed as proof of causation. A positive association is not equal to a causal relationship. Moreover, the hospital-based case-control studies did not show a statistically significant increased risk of ovarian cancer from reported perineal talcum powder use.

As an example, people who carry a lighter have a higher risk of developing lung cancer because there is an association between those who carry a lighter and the incidence of lung cancer. But it becomes apparent that it is not the lighter itself that causes lung cancer, but rather cigarette smoking (with which carrying a lighter is correlated) that is the cause. There are numerous such examples in public health topics and medical practice. The key point is that all scientists and physicians must try to establish the true cause of a disease by excluding the many confounding factors associated with ovarian cancer.

One meta-analysis (cited by Dr. Saed) is Huncharek et al., 2003. Although there appears to be a 33% increased risk of ovarian cancer in women who reportedly used perineal talc powder after meta-analysis of a total of 11,933 study subjects, the authors from this study stated (in the conclusion of the article) that "*[t]he available observational data do not support the existence of a causal relationship between perineal talc exposure and an increased risk of epithelial ovarian cancer. Selection bias and uncontrolled confounding may account for the positive associations seen in prior epidemiological studies*" (Huncharek et al., 2003).

Articles like these reflect the understanding by researchers that many confounding factors may exist in assessing the association between talc powder and ovarian cancer that have not yet been definitively identified.

A related problem is that the results of case control studies are prone to recall bias. This was shown in the Schildkraut study (Schildkraut et al., 2016), but could well have affected studies

before 2014 as well. Thus, even those authors who published studies finding a positive (but very modest) association between talc and ovarian cancer also cautiously mentioned the limitation of their own studies. As an example, in one very recent published paper, the authors concluded that the "*fact that the association between genital talc use and risk of ovarian cancer is present in case-control, but not in cohort studies, can be attributed to bias in the former type of studies*" (Berge et al., 2018).

In light of the limitations in the research, scientists remain skeptical of a causal connection between talc use and ovarian cancer, even if they take a precautionary approach in their own practice. A recent article relied on by plaintiffs' experts noted that : "*[t]here is a substantial need for further research on a potential mechanism by which ovarian cancer may be caused by talc, as this will allow a causal relationship to be established or rejected with more certainty*" (Penninkilampi and Eslick, 2018). Dr. Saed's research does not fill this void because it neither establishes nor rejects the hypothesis of a causal link between talc use and ovarian cancer.

5. Another issue concerning epidemiologic studies is that almost all reports apparently lumped all types of ovarian cancer together in their analyses. It has been well established that ovarian cancer is a highly heterogeneous group of diseases that can be broadly classified as Type I and Type II diseases (Kurman and Shih Ie, 2016; Shih and Kurman, 2004). In other words, various types of ovarian cancer are characterized by distinct clinicopathological and molecular features. Moreover, their origins and risk factors are all different.

Briefly, Type I ovarian cancers include clear cell carcinoma, endometrioid carcinoma, mucinous carcinoma and low-grade serous carcinoma. In addition to their unique histologic appearances, they are characterized by somatic mutations in PTEN, ARID1A, KRAS, PIK3CA. Both clear cell carcinoma and endometrioid carcinoma are mostly derived from previous endometriotic cysts of the ovary (or ovarian endometrioma), and the presence of ovarian endometriotic cysts carries the risk of developing both types of Type I ovarian cancer.

By contrast, Type II ovarian cancer includes high-grade serous carcinomas, the most common and aggressive type of ovarian epithelial neoplasms. Type II ovarian cancer is generally referred to as "ovarian cancer" in public because it is the most common and lethal type. In contrast to Type I ovarian cancers, high-grade serous carcinomas demonstrate a high level of proliferative activities and genomic instability, as reflected by abnormal mitoses and micronuclei. They almost all harbor TP53 mutations, but not the same type of mutations found in Type I ovarian cancers.

The risk factors of Type II ovarian cancer include the lifelong accumulated number of ovulations (so, child-bearing, oral contraceptive use and breast-feeding reduce the risk (Langseth et al., 2007)) and the germ-line mutation of BRCA1 and BRCA2 genes, which are not the same as the risks in Type I diseases. As compared to Type I ovarian cancers, the majority of Type II ovarian cancers are diagnosed late and therefore the clinical outcome of women suffering from Type II ovarian cancers can be dismal, requiring surgery and chemotherapy, and often resulting in death. Although more recently, the PARP inhibitor has been approved by the FDA to treat BRCA-mutated ovarian high-grade serous carcinomas and has been established as a

maintenance therapy in newly diagnosed advanced ovarian cancer (Moore et al., 2018), a cure for this devastating disease is still not within reach.

From this perspective, the question of whether perineal use of talc powder is related to ovarian cancer should be re-phrased more specifically as whether the talc use is associated with Type I or Type II diseases. Without specifying the tumor types in these cases, it would be difficult to start looking into this question in a scientific way. It is possible that, even if talc users have a higher than average risk in developing certain subtypes of ovarian cancer, the risk might not be the same for all types, or there is no association with some subtypes at all. If different subtypes of ovarian cancer are included as one group, it would be highly challenging to determine if talc is a carcinogen and cause of ovarian cancer or not because there are different diseases under the rubric of "ovarian cancer."

6. The claim that talc powders can cause chronic inflammation, which can lead to the development of ovarian cancer (as proposed by Dr. Saed) is significantly flawed for at least two reasons. One is the lack of cogent evidence that talc depositions in humans are associated with chronic inflammation in normal fallopian tubes and ovaries. In a study of human ovarian tissues, researchers found no evidence of response to talc, such as foreign body giant cell reaction and/or fibrosis, and in addition found no correlation between clinical talc exposures and actual tissue talc deposition levels (Heller et al., 1996).

In experiments involving rats, applying talc powder induced genital infection (likely due to the non-sterile nature of the talc or control saline used and experimental procedure) (Keskin et al., 2009). According to the authors, no peritoneal change was observed. Thus, the forced application of talc powder into the murine genital tract artificially induced bacterial infection, which was not seen in humans, as there are no data reporting perineal talc powder use induces genital infection.

Moreover, as compared to the murine genital tract, the human fallopian tube and ovary are "far" away from the perineum. The talc powder applied to the perineal area technically needs to travel remotely to reach the fallopian tube and ovary through the vagina, cervix, and endometrial cavity. Importantly, young women who use talc powder usually have an enclosed cervix (the function of which is to prevent foreign bodies and microorganisms from coming into the uterine cavity, which is normally sterile). And even if talc powders can really arrive at the endometrial surface, the menstruation that sheds endometrial tissue off outside the body will clear these powders.

The second flaw in the inflammation theory is that if talc deposition is indeed a cause of chronic inflammation, such inflammatory background is not sufficient to cause cancer. A recent study shows that pelvic inflammatory disease (PID) was associated with an increased risk of borderline ovarian tumors, but not ovarian cancer in general. Although the results of this study suggest a histotype-specific association with PID, the association of PID with ovarian cancer risk is still somewhat uncertain and requires further investigation (Rasmussen et al., 2017). Also, in the literature, salpingitis or inflammation in the pelvis was not associated with ovarian cancer risk (Parazzini et al., 1996). Based on my own study and observation, I did not detect significant increase in chronic salpingitis in fallopian tubes containing the precursor ovarian cancer lesions. It would be critically important to the inflammation theory to associate chronic inflammation and

the occurrence of ovarian cancer precursors in the fallopian tubes – and to rule out the possibility that ovarian cancer itself induces chronic inflammation in normal tissues.

In reality, chronic inflammation observed in ovarian cancer is most likely a result of cancer, not the cause. My recent study, which is included in full at the end of this report, offers significant support for this conclusion. I reviewed samples of fallopian tissue taken from women with pre-cancerous lesions that had not yet developed into ovarian cancer, as well as from healthy women (to serve as negative controls) and from women with ovarian cancer (to serve as positive controls). My results showed that ovarian cancer precursor lesions, prior to the development of cancer, are not associated with inflammation, while ovarian cancer cases are associated with inflammation, strongly indicating that inflammation follows, but does not cause, ovarian cancer. There are several reasons why invasive carcinoma like ovarian cancer is associated with inflammatory background within cancer tissue and nearby tissue, and they include new antigens produced by the cancer cells (due to mutations) and cancer cell-induced inflammation related molecules. Because there is no evidence of this association between chronic inflammation and occurrence of tubal precursors, and, indeed, evidence to the contrary, the claim that talc deposition causes chronic inflammation, which subsequently causes ovarian cancer, is unsustainable.[2]

7. In any event, even assuming some role for inflammation in the development of ovarian cancer, it is important to distinguish between what is necessary and what is sufficient to cause cancer. In several human cancers, chronic inflammation is associated with the initiation of malignant changes in the tissues because of the oxidative stress that may damage DNA and cause mutations (such as TP53). Therefore, in those cancer types (such as prostate cancer and certain types of gastric cancer), chronic inflammation is required to induce tumor formation but itself is not sufficient to induce cancer development. This argument is supported by numerous reports showing that even chronic inflammation is related to cancer development; the chance to develop cancer in the chronic inflammatory background is still uncommon and most importantly, the risk is tissue type dependent. In other words, there are many endogenous and exogenous factors that can promote chronic inflammation, including aging, chronic infection and even mental stress, among others. Thus, even if there is a chronic inflammation near the ovarian precursor lesions in fallopian tubes (and in fact there is no such evidence), it still remains unclear whether this inflammation is related to talc deposition or results from other factors such as infection, aging, etc.

8. Another frequently cited study by Cibula et al. reported that tubal ligation was associated with a reduced risk for ovarian cancer (Cibula et al., 2011). The results from this study have been used by advocates who believe talc is a carcinogen to explain the blockage of talc deposition to the ovary through the fallopian tubes as a possible mechanism for the observed decrease in ovarian cancer. However, as previously mentioned, perineal use of talc powder is, at most, equivocally

[2] In a published report entitled "Does long-term talc exposure have a carcinogenic effect on the female genital system of rats? An experimental pilot study," the authors concluded that "Talc has unfavorable effects on the female genital system. However, this effect is in the form of foreign body reaction and infection, rather than being neoplastic" Keskin, N., Teksen, Y.A., Ongun, E.G., Ozay, Y., and Saygili, H. (2009). *Does long-term talc exposure have a carcinogenic effect on the female genital system of rats? An experimental pilot study*. Arch Gynecol Obstet 280, 925-931.

(and inconsistently) associated with ovarian cancer risk in some retrospective case-control studies. A prospective population-based study (study of 121,700 registered nurses in the USA who were aged 30-55 years at enrollment in 1976) in the Nurses' Health Study does not identify any significant association between perineal talc use and ovarian cancer risk overall (Gertig et al., 2000). There are two alternative mechanisms accounting for the protective effect of tubal ligation. First, assuming it is true that migration of non-motile particles up the fallopian tubes is feasible, some of the ovarian cancers might be imported from the uterine cavity, where the primary tumors arise in the endometrium, and not in the fallopian tube or ovary. The tumor cells arising from the endometrium (both endometrioid and serous types) can readily travel through the fallopian tubes to reach the ovaries, which provide a suitable microenvironment for tumor cells to grow as an "ovarian" cancer. Therefore, tubal ligation can effectively block the passage of uterine cancer to the ovary. In fact, the authors on Cibula's paper also concluded in the end that the results of this meta-analysis should provide an impulse for further research on the etiology of ovarian epithelial cancers, focusing particularly on the importance of retrograde transport of endometrial cells. The other explanation is due to the surgery-induced anatomic alteration of the tubal fimbriated ends, which are no longer intimately associated with the ovulation sites of the ovary (Roy et al., 2005). Thus, the follicular fluid that is proposed to be carcinogenic (Huang et al., 2015) would not directly splash onto fallopian tube fimbrial ends, reducing the carcinogenic events of fallopian tube epithelium and preventing the occurrence of ovarian cancer precursor lesions on the fallopian tubes.

In summary, there is no relevant and cogent evidence based on the published literature, Dr. Saed's research and my own research to prove that cosmetic talc use can cause ovarian cancer. Among the steps that remain unproven are migration to the ovaries, the induction of chronic inflammation or oxidative stress, and evidence that these events are carcinogenic or precursors to ovarian cancer.

D. Undisclosed conflicts of interest affecting Dr. Saed's work

Dr. Saed testified at his deposition that he billed the time he spent preparing his manuscript to lawyers for Beasley Allen. (Saed Dep. vol. 1, 33:22-24.) The precise nature of the arrangement is unclear; he claims that his university paid for some of the lab work that was the basis for the manuscript (Saed Dep. vol. 1, 34:2-39:9), but his hours in total spent on preparing his opinion and in writing the paper are not compatible with what he was paid in sum. It is also uncertain whether Dr. Saed also disclosed his relationship with Beasley Allen to his coauthors and institution.

Regardless of the details of the arrangement, the important point is that Dr. Saed failed to adequately disclose the resulting conflict of interest. Normally, experiments and the time spent in writing research articles are part of an author's academic responsibility and are supported by research grant(s) or institutional support. To charge the time spent in preparing an article is unusual and could potentially introduce a bias into the research results. Relatedly, conflicts of interest can compromise objectivity. This can occur not only in performing the experiments but also in writing the research paper in a manner that slants toward the authors' favored conclusions.

There are indications that objectivity was compromised here. For example, it is unclear to what extent Beasley Allen influenced the design or conduct of the experiments. In his deposition, Dr. Saed was asked, "*[w]ith regard to the tests that were part of the manuscript, those tests were done in connection with your communications with Beasley Allen, correct?*" (Saed Dep. vol. 1, 63:9-11.) He acknowledged that he had communicated the details of his experiment to the firm, though he also insisted that the design of it was his alone. ("*A. I actually designed this whole thing. So when they approached me and I got -- you know, I told them this is what I'm going to do, this is what I have in mind, we have all this setup in my lab and I want to do it, and I did it*" Saed Dep. vol. 1, 67:17-21.) This insistence provides little comfort. Based on my experience in academia for 30 years, it is unusual for any scientist to communicate with a non-academic party in any form during experiments because there is no such need; thus, Dr. Saed's departure from that norm necessarily raises questions about his motivations for sharing the details of his experiment with his financiers. It also raises a question about why the firm paid Dr. Saed for his writing of the paper since it would normally be incumbent upon Dr. Saed within the scope of his academic obligations to finish the writing and publish it himself.

One other significant indicator that Dr. Saed's objectivity may have been compromised is the language used in the manuscript. There are a number of ways an author can write up the same results, and the choice of language can profoundly affect the general reception of the readers based on the conclusions the author chooses to emphasize and those he or she chooses to downplay or ignore. It is obvious to me, from my perspective as an author who has contributed significantly to the literature and as a frequent journal reviewer, member of several editorial boards and the prior editor-in-chief of a medical journal (*Current Obstetrics and Gynecology Report*, 2012-2015), that Dr. Saed's paper has intentionally underscored the supposedly contributing role of talc to ovarian carcinogenesis, despite the fact that the claim is not supported by his data at all. In addition, Dr. Saed, unlike other authors, did not discuss the limitations in interpreting his results at all in the paper, which is a very unusual practice in scientific reports.

As a result, it was especially important for Dr. Saed's conflict-of-interest statement to completely disclose the nature and purpose of his financing. Based on his deposition, I think it is clear that he did not follow best practices in scientific reporting because he failed to disclose the relationship with a law firm involved in litigation concerning the same subject matter as the manuscript, either in the conflict-of-interest statement or in his communications with the journal that has accepted his manuscript for publication.

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F. Materials Relied Upon

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Study Report to Determine Whether Chronic Inflammation Causes Ovarian Cancer

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Study location: 1550 Orleans Street, CRB-II, Rm 305, Baltimore, Maryland 21231

Time frame: 1/1/2019 to 2/11/2019

Hypothesis: Chronic inflammation has been thought to be carcinogenic in several types of human cancer including those arising from esophagus, colon, pancreas, prostate and liver. On the other hand, many cancer types are thought not to be related to chronic inflammation, including those developing from brain, connective tissue, etc. There is no evidence that ovarian cancer development is indeed caused by chronic inflammation. We hypothesize that if ovarian cancer development is caused by chronic inflammation from various etiologies, one should observe at the human tissue level that the very early lesions of ovarian cancer, i.e., ovarian cancer precursors (before ovarian cancer arises), should be accompanied by chronic inflammation in close geographical proximity to the precursor lesions.

Question to ask: To determine whether ovarian cancer precursors, especially those without concurrent ovarian cancer, are associated with chronic inflammation.
The early molecular events of ovarian carcinogenesis remain poorly understood, resulting in a lack of effective prevention and early detection strategies (Skates et al., 2017; Trabert et al., 2017). Unlike cancers arising in organs such as the colon, where the early events of carcinogenesis can be studied because their precursor lesions are well-recognized, the precursors of ovarian high-grade serous carcinoma (HGSC), the most common and lethal type of ovarian cancer, have eluded detection until recently. Accumulating evidence suggests that serous tubal intraepithelial carcinoma (STIC) or its precursor lesions, including p53 signature and serous tubal intraepithelial lesion (STIL), located at fallopian tubes or cortical inclusion cysts of the ovary, are the precursors of ovarian HGSC (Ducie et al., 2017; Kindelberger et al., 2007; Kuhn et al., 2012a; Kuhn et al., 2012b; Kuhn et al., 2012c; Kuhn et al., 2012d; Kuhn et al., 2010; Kuhn et al., 2016; Kuhn et al., 2012e; Lee et al., 2006; Lee et al., 2007; Medeiros et al., 2006; Piek et al., 2001a; Piek et al., 2001b; Sehdev et al., 2010; Vang et al., 2012b; Visvanathan et al., 2017). The reported incidence of tubal lesions varied in the literature, but when a rigorous sampling was performed in a large cohort of fallopian tubes from a high-risk population, the incidence of p53 signature and STIC/STIL can be as high as 27% and 12%, respectively (Visvanathan et al., 2018).

Microscopically, STICs exhibit significant nuclear atypia and architectural alterations, *TP53* mutations and high proliferative/apoptotic activity. STIC cells are often loosely arranged and can readily disseminate outside the fallopian tube. The p53 signature is identified as a stretch of 12-30 normal-appearing epithelial cells having a p53 immunoreactivity pattern compatible with a missense *TP53* mutation and displaying low proliferative activity, similar to adjacent normal tubal epithelium. The term STIL has been used to describe, among other lesions, a group of tubal precursors characterized by lower levels of nuclear atypia than STIC, p53 staining patterns

compatible with either missense or deleterious TP53 mutations, and a level of proliferative activity similar to adjacent normal epithelium (Vang et al., 2012a; Visvanathan et al., 2011). "Dormant STICs" in this study were deemed morphologically compatible with STILs by a panel of gynecologic pathologists. Although molecular relationships between STICs and concurrent ovarian HGSCs have been reported (Eckert et al., 2016; Kuhn et al., 2012b; McDaniel et al., 2015; Rabban et al., 2015; Singh and Cho, 2017; Visvanathan et al., 2017), few of these studies analyzed p53 signatures or STILs, largely because of technical challenges. More importantly, since all of these studies analyzed patients with tubal lesions co-existing with advanced ovarian HGSCs, it is likely that some of these lesions were disseminated tumor cell clones from the adjacent, concurrent ovarian tumors, therefore obscuring the evolutionary histories. This issue is aggravated in ovarian HGSCs, which are often diagnosed late, at which time the vast late-stage tumor mass overwhelms or effaces the precursor lesions located at either the fallopian tube or the small cortical inclusion cysts of the ovary, leaving little trace of the molecular landscape existing before the advent of invasive cancer. Indeed, a recent article cautioned against clonal evolution studies performed on advanced tumors with high genetic heterogeneity and the possibility of constituent clones arising from multiple cell lineages (Alves et al., 2017). Consequently, distinguishing between true precursor lesions and HGSC implants is problematic (Rabban et al., 2015; Singh and Cho, 2017). Nevertheless, powerful techniques for analysis of clonal evolution are useful for assessing clonal relationships between primary tumor and distant metastases and when true precursor lesions are available, the same tools can provide similarly powerful means to delineate tumor evolution (Wu et al., 2018).

Study design and case selection: The cases were retrieved from the archival files from the ovarian cancer precursor registry supported by the US Department of Defense (USAMRMC), Directed Medical Research Programs (CDMRP), grant title: "Prevention of Ovarian High-Grade Serous Carcinoma by Elucidating Its Early Changes," grant number: W81XWH-11-2-0230. The purpose of this completed study is to determine the origin and pathogenesis in the development of ovarian high-grade serous carcinomas by employing cancer genetics, cell biology, animal models and epidemiologic studies through a multi-institutional research effort. The consortium includes five research projects and three cores. Tissue collection started as early as 2013. This archival file contained 48 cases of ovarian cancer precursors, carcinoma and normal fallopian tubes, and their diagnoses were made after a prior pathology review by a panel of gynecologic pathologists. Many research projects have utilized this and its related resources (please see the attached information), resulting in peer-reviewed publications. This indicates that this tissue source is useful and reliable to study projects related to ovarian cancer pathogenesis.

In particular, I identified the cases showing ovarian cancer precursor lesions without concurrent ovarian cancer. I also selected a few cases of ovarian cancer as the controls. I excluded those cases showing active bleeding (the presence of inflammatory cells due to hemorrhage can confound the interpretation). Once identified, I retrieved the slides, including H&E, and accompanied immunostaining slides. All cases are anonymous, without patients' personal identifiers (but labeled with experimental ID). I re-reviewed and recorded results and took representative photomicrographs using a Nikon Eclipse Ci light microscopy and Nikon digital camera. Images were taken at either 20X or 40X when appropriate. A total of 59 lesions and areas of interest from 48 individuals were included in this study. The review of the slides took place in the Cancer Research Bldg,- II, Room 305 at the Johns Hopkins Medical Institution,

Baltimore, Maryland, from February 2 to February 18, 2019.

Diagnosis criteria: I used the criteria to diagnose ovarian cancer precursor lesions as summarized in the research papers of which I am one of the coauthors (Vang et al., 2012a; Visvanathan et al., 2011). To determine if the precursor lesions are associated with chronic inflammation, I use lymphocyte infiltration in the stroma and or within the epithelium of the lesion on either H&E stained or immunohistochemically stained slides. To better demonstrate chronic inflammation in tissues, I also used positive control slides showing increased lymphocytic infiltrate as the references. To conclude that there is a chronic inflammation, I must observe a significant increase in lymphocyte density within the lesion or in its immediate stromal tissue as compared to the background normal-appearing fallopian tube epithelium without precursor lesions or carcinomas. Alternatively, fused plicae of the fallopian tube papillae can also be considered as evidence of prior salpingitis (chronic inflammation in fallopian tube) in appropriate cases. To compare the lymphocyte density between lesion and normal epithelial areas is important, as there is a normal immune surveillance in normal fallopian tube mucosa containing the resident immune cells, including lymphocytes (Ardighieri et al., 2014). I diagnose chronic inflammation based on my training as a pathologist and experience practicing gynecologic pathology for 20 years. The criteria used here is no different from those in my clinical practice.

Research findings: After identifying those qualified cases, I organized them into individual slide holders (one case in one folder). First, I used the low-power lens (4X) to look for the regions of interest, followed by higher-power lenses, including 10X, 20X and 40X on H&E slides. For p53 signature cases, I used p53 antibody stained slides since the H&E stain will not allow one to identify p53 signatures. I recorded the diagnosis and evaluated the density of chronic inflammatory cells, i.e., lymphocytes on the slides on H&E and/or immunostained slides. I compared the lymphocyte density between the lesion and the background normal-appearing fallopian tube mucosa. I then took photomicrographs on the lesions or regions of interest (usually at 20X) and saved the image files as .jpg files in my desktop computer in a folder. I labeled the file names of each image using the original experimental ID to avoid confusion.

My study result was summarized in the following **Table 2**. A total of 59 areas of interest were analyzed, and they included 18 p53 signature lesions, 25 STICs, eight normal fallopian tubes and eight ovarian (high-grade) serous carcinomas. Based on intraepithelial and intra-stromal lymphocyte density, as well as the architecture of tubal plicae, I did detect chronic inflammation in carcinoma tissues (the positive controls). When I applied the same criteria, I did not observe chronic inflammation in the p53 signatures and STIC lesions as compared to their background normal-appearing fallopian tube mucosa in any of the cases examined. **The photomicrographs are attached as an appendix**, and one can see that there are two types of images presented. One is conventional H&E slides to show the STICs and the other is immunohistochemistry (mostly p53 staining) to demonstrate p53 signatures, because without p53 staining, p53 signature lesions could not be identified by H&E staining. Immunohistochemistry using immune cell markers was not performed because it is not required to do so in routine diagnostic pathology, although chronic inflammation can be validated by immunostaining to highlight immune cells. Although not required, every board-certified anatomic pathologist now learns how to perform this procedure as part of his or her training. I also focused on comparing the lymphocyte density

between a lesion and its immediately adjacent normal region whenever the junctions were available for study. As a result, I did not see the difference between the lesion and the adjacent normal areas in terms of increased level of lymphocytic infiltration. Besides, there is a heterogeneity of lymphocyte density within normal fallopian tube mucosa with unknown significance; therefore, I used the average of lymphocyte density from normal fallopian tube mucosa to compare to those in fallopian tube precursor lesions.

In this study, I also ask whether there is any difference in lymphocyte density in mucosae (the connective tissue layer beneath the tubal epithelium) between normal fallopian tubes and those fallopian tubes harboring ovarian cancer precursor lesions (but without ovarian cancer). For the former, I selected eight new cases (10028, 10031, 10039, 10052, 20001, 20001, 20003, 20004), together with 10 previously reported cases (Ardighieri et al., 2014) (for a total of 18 normal-appearing fallopian tubes). As a result, there is no evidence that either group has an apparent increase in lymphocytes in mucosae. Like the fallopian tubes harboring precursor lesions, normal fallopian tubes do not have chronic inflammation.

Interpretation and Discussion: Based on the data presented, I attest that ovarian cancer precursor lesions, including STIC and p53 signatures (before cancer develops), are not associated with increased lymphocyte infiltration, and thus there is no evidence of chronic inflammation. This new result refutes the hypothesis that chronic inflammation can cause the malignant transformation of fallopian tube epithelium into cancer precursor lesions. If the precursor lesions are not the result of chronic inflammation, ovarian cancer is not caused by chronic inflammation because ovarian cancer (the invasive cancer) must derive from its precursor (i.e., p53 signatures and STICs), just like all other human cancers. Similarly, a recent study published by Malmberg et al. did not find evidence that chronic inflammation or tubal injury is involved in the carcinogenesis of ovarian cancer (Malmberg 2016).

Unlike cancers arising in organs such as the colon, where the early events of carcinogenesis can be studied because their precursor lesions are well-recognized, the precursors of ovarian high-grade serous carcinoma (HGSC), the most common and lethal type of ovarian cancer, have eluded detection until recently. Accumulating evidence suggests that serous tubal intraepithelial carcinoma (STIC) or its precursor lesions, including p53 signature and serous tubal intraepithelial lesion (STIL), located at fallopian tubes or cortical inclusion cysts of the ovary are the precursors of ovarian HGSC (Kurman and Shih Ie, 2016; Kurman and Shih, 2010) (Wu et al., 2018). The reported incidence of tubal lesions varied in the literature, but when a rigorous sampling was performed in a large cohort of fallopian tubes from a high-risk population, the incidence of p53 signature and STIC/STIL can be as high as 27% and 12%, respectively (Visvanathan, 2018).

One may ask why this study focuses on determining the chronic inflammation in precursor lesions rather than in ovarian cancer. This is because if the study analyzed patients with tubal lesions co-existing with advanced ovarian high-grade serous carcinomas, it is likely that some of these lesions were indeed the disseminated tumor cell clones from the adjacent, concurrent ovarian tumors, therefore obscuring the evolutionary histories. This issue is aggravated in ovarian HGSCs, which are often diagnosed late, at which time the vast late-stage tumor mass overwhelms or effaces the precursor lesions located at either the fallopian tube or the small

cortical inclusion cysts of the ovary, leaving little trace of the molecular landscape existing before the advent of invasive cancer. More importantly, cancer often induces chronic inflammation due to the neo-antigens (due to many missense mutations that produce new epitopes of proteins) that trigger immune responses in tissues. In this case, it is unknown if the chronic inflammation associated with cancer is the cause of the cancer or the result of it. All things considered, the best experimental approach is to directly observe the precursor lesions and detect if chronic inflammation is present. If yes, the development of ovarian cancer can be causally induced by chronic inflammation. Otherwise, the chronic inflammation that always occurs in ovarian cancer is not the cause of carcinogenesis of ovarian carcinoma. So, the final answer from this study is that ovarian cancer precursor lesions are not associated with chronic inflammation, thus refuting the hypothesis that chronic inflammation is the cause of ovarian cancer.

In conclusion, the most plausible cause of ovarian (high-grade) serous carcinoma is related to the incessant ovulation theory, which posits that the accumulated numbers of ovulations increase the risk. This risk is substantially further enhanced by genetic predisposition, including BRCA1/2 germline mutations. Temporary cessation of ovulation, such as during pregnancy or while taking birth control, is known to have a significant protective effect with respect to ovarian cancer (Bera, 2008), and the mechanism of this effect is revealed by recent advances in this study field. Previous studies have examined the link between ovulation and cancer development by examining fallopian tube follicular fluid (FF), which bathes fallopian tubes after each ovulation and is a required process during ovulation (Bahar, 2014) (Hsu, 2015). Scientists found that FF in high concentrations could cause significant DNA damage, double-stranded breaks, and TP53 nuclear accumulation that created an immunostaining pattern similar to that seen in p53 signature. Reactive oxygen species (ROS) and the IGF2 have been implicated in this mutagenesis (Hsu, 2015) (Hsu, 2019).

Lesion	case ID	diagnosis	with concurrent cancer	inflammation*
1	S80001	p53 sig	no	no
2	S80002	p53 sig	no	no
3	S80003	STIC	no	no
4	S80004	p53 sig	no	no
5	S80005	p53 sig	no	no
6	S80006	p53 sig	no	no
7	S80007	STIC	no	no
8	10150	STIC	no	no
9	10149	p53 sig-1	no	no
10	10149	p53 sig-2	no	no
11	10148	p53 sig	no	no
12	10147	STIC	no	no
13	10146	STIC	yes	no
14	10146	ovarian cancer	yes	yes
15	10145	p53 sig	no	no
16	10144	STIC	no	no
17	10142	p53 sig	yes	no
18	10142	ovarian cancer	yes	yes
19	10141	STIC	yes	no
20	10141	ovarian cancer	yes	yes
21	10137	STIC-1	no	no
22	10137	STIC-2	no	no
23	10136	STIC	no	no
24	10135	STIC	no	no
25	10133	STIC	no	no
26	10060	STIC	no	no
27	10059	STIC	no	no
28	10058	ovarian cancer	yes	yes
29	10058	STIC	yes	no
30	10057	ovarian cancer	yes	yes
31	10056	STIC	no	no
32	10055	ovarian cancer	yes	yes
33	10053	STIC	yes	no
34	10013	STIC-1	no	no
35	10013	STIC-2	no	no
36	10013	STIC-3	no	no
37	10013	p53 sig	no	no
38	30032	STIC	no	no
39	20073	STIC	no	no
40	10046	p53 sig	no	no
41	20055	ovarian cancer	yes	yes
42	20055	STIC	yes	no
43	10022	p53 sig	no	no
44	10020	p53 sig	no	no
45	10043	p53 sig	no	no
46	10018	p53 sig	no	no
47	10026	p53 sig	no	no
48	10013	p53 sig	no	no
49	20114	STIC	yes	no
50	20114	ovarian cancer	yes	yes
51	10011	STIC	no	no
52	10028	NFT	no	no
53	10031	NFT	no	no
54	10039	NFT	no	no
55	10052	NFT	no	no
56	20001 NFT	NFT	no	no
57	20002 NFT	NFT	no	no
58	20003 NFT	NFT	no	no
59	20004 NFT	NFT	no	no

*Inflammation is defined by increased lymphocytic infiltrate associated with the lesions as compred to the background normal tissues or mucosa.

Table 2. The summary of the results.

Appendix

Publications supported by DoD Ovarian Cancer Consortium (OCPR: W81XWH-11-2-0230)

Title: Prevention of Ovarian High-Grade Serous Carcinoma by Elucidating Its Early Change

2011-Current (all investigators in this consortium)

6.1. Journal publications (with acknowledgement of federal support)

1. George SH, Greenaway J, Milea A, Clary V, Shaw S, Sharma M, Virtanen C, Shaw PA: Identification of abrogated pathways in fallopian tube epithelium from BRCA1 mutation carriers. J Pathol 2011, 225:106-17 PMID: 21744340.

2. Kurman RJ, Shih Ie M: Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer--shifting the paradigm. Hum Pathol 2011, 42:918-31 PMCID: PMC3148026

3. Kurman RJ, Vang R, Junge J, Hannibal CG, Kjaer SK, Shih Ie M: Papillary tubal hyperplasia: the putative precursor of ovarian atypical proliferative (borderline) serous tumors, noninvasive implants, and endosalpingiosis. Am J Surg Pathol 2011, 35:1605-14 PMCID: PMC3193599

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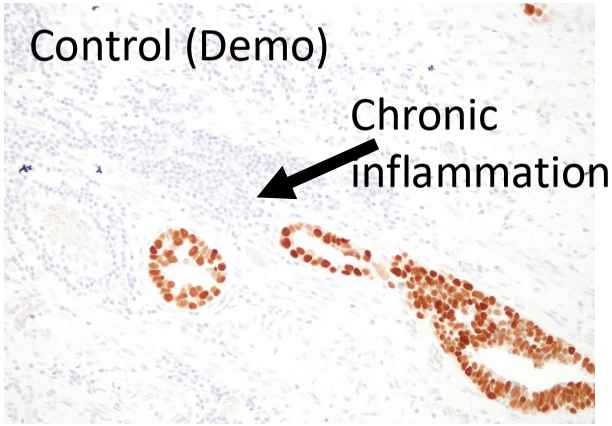
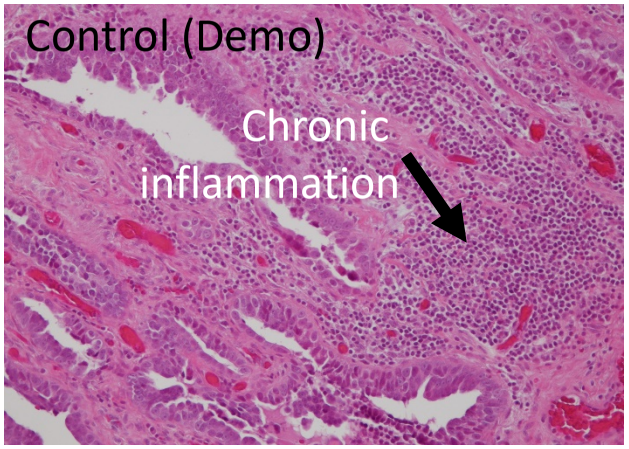
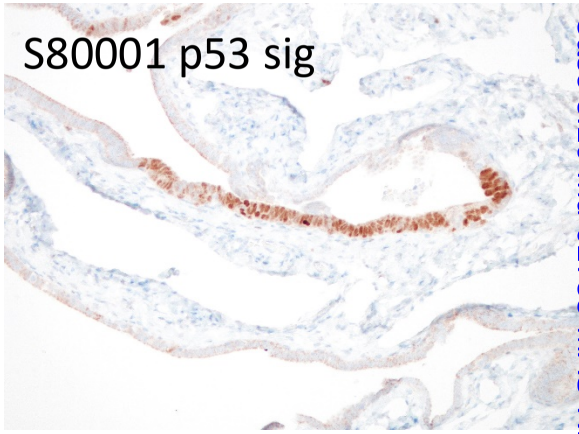
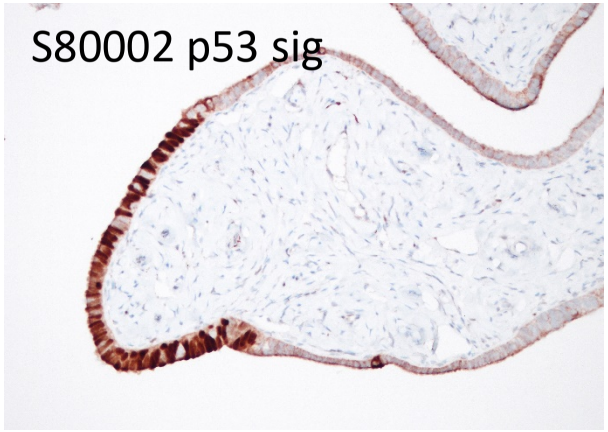
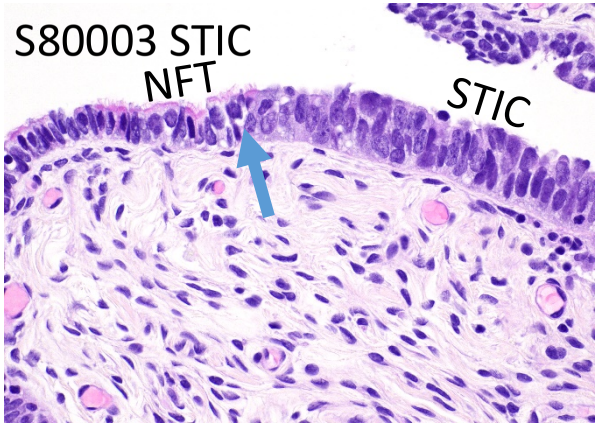
Appendix: Photomicrographs

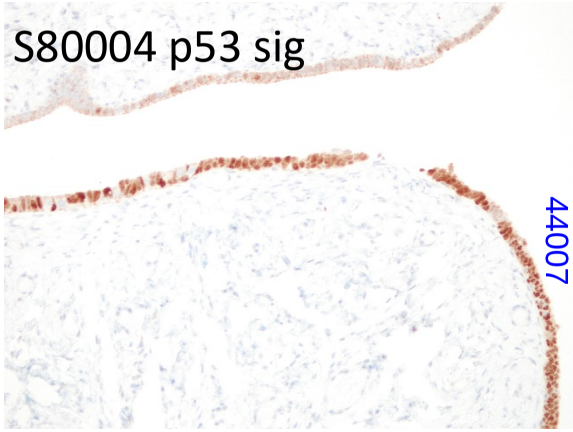


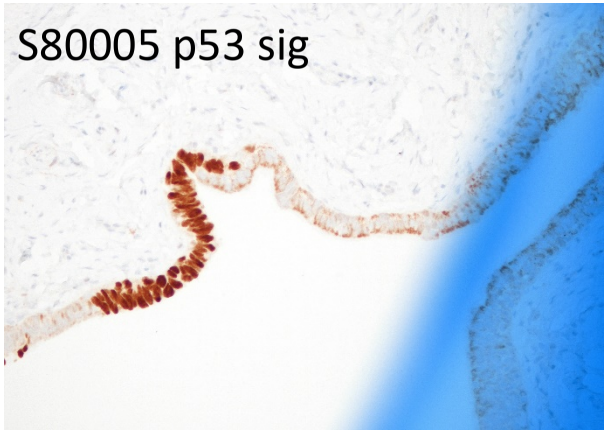


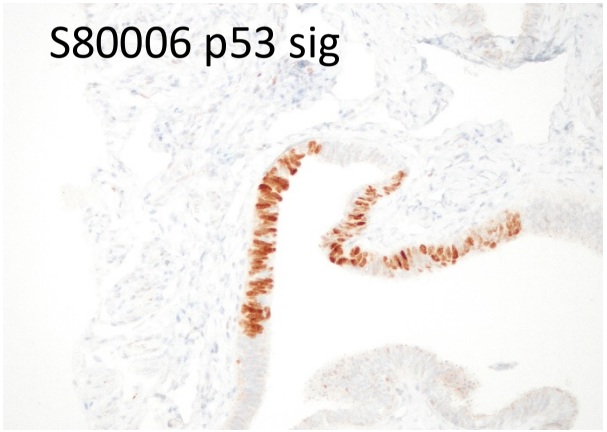


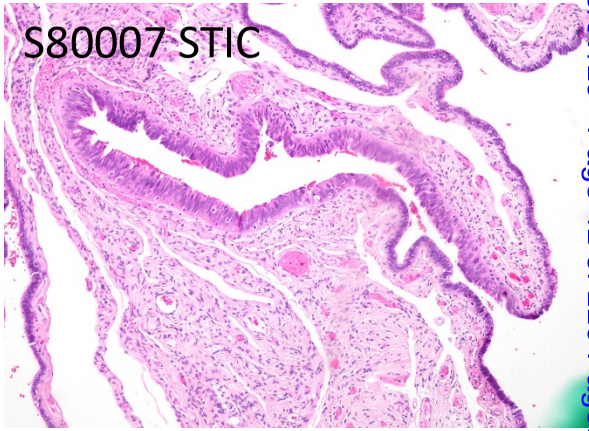


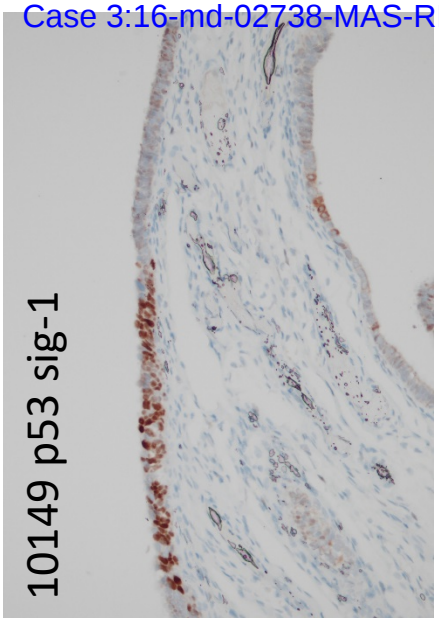


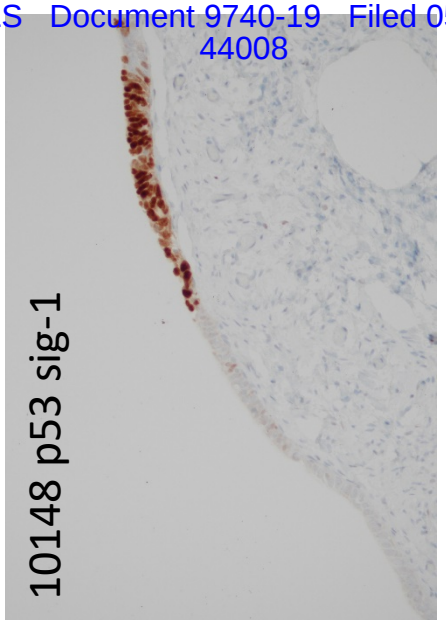


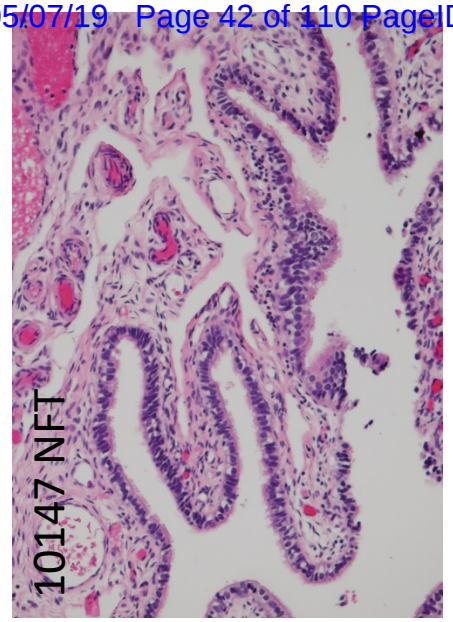


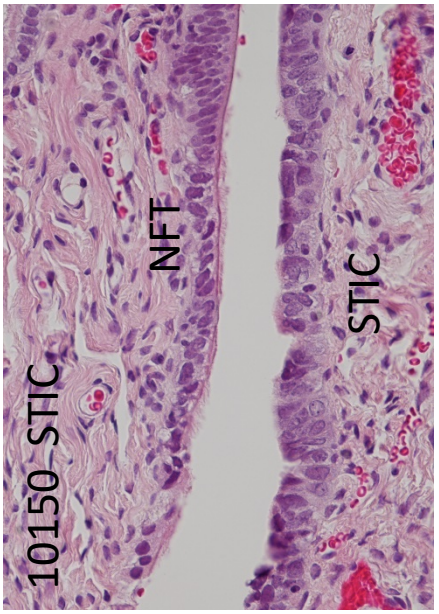





10149 p53 sig-1


10148 p53 sig-1


10147 NFT


10150 STIC
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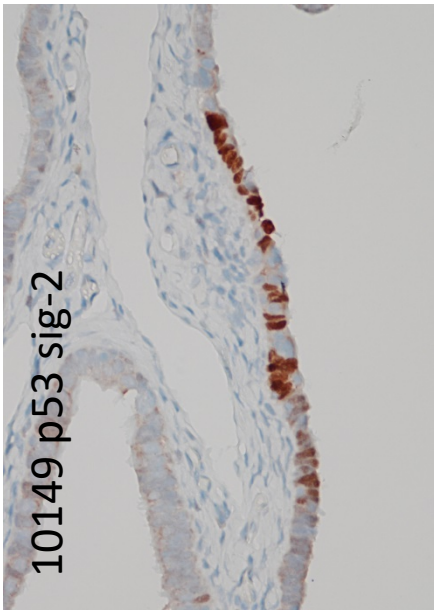
STIC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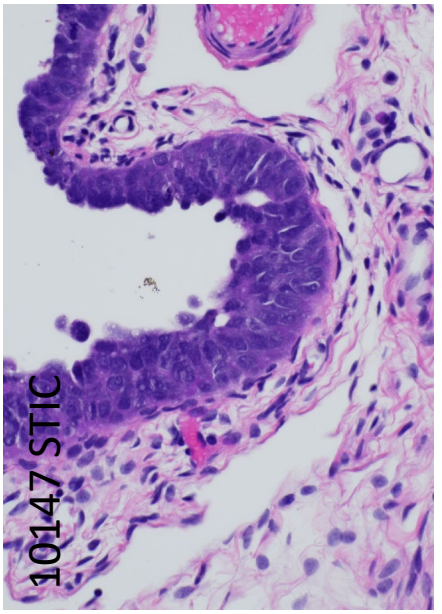
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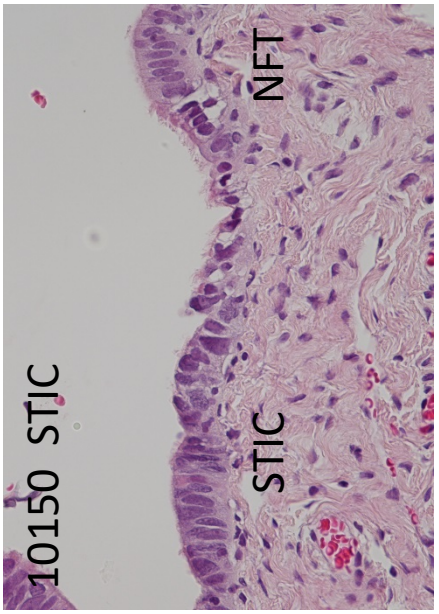
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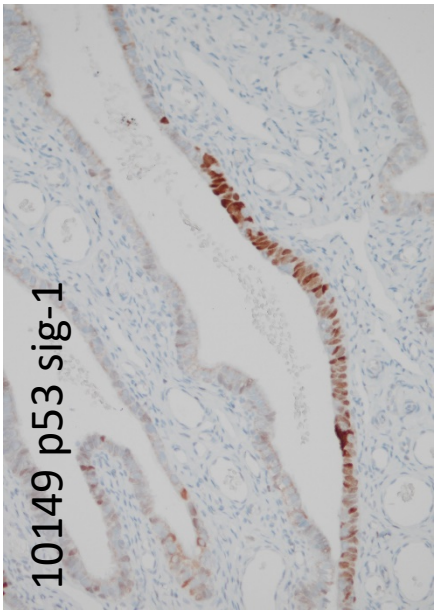
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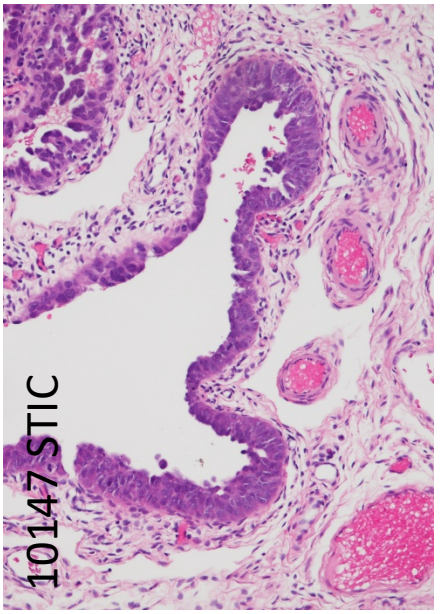
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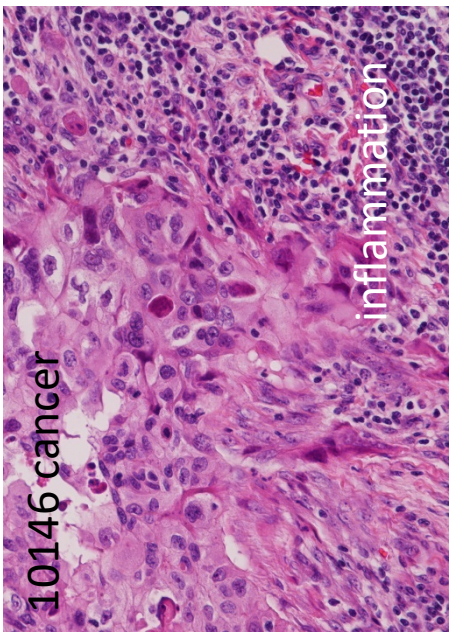
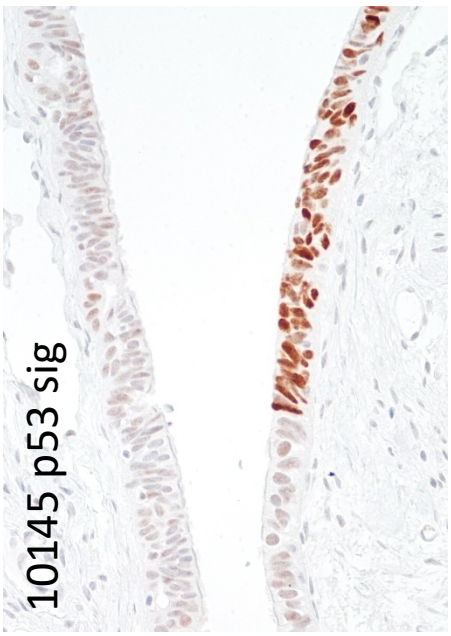
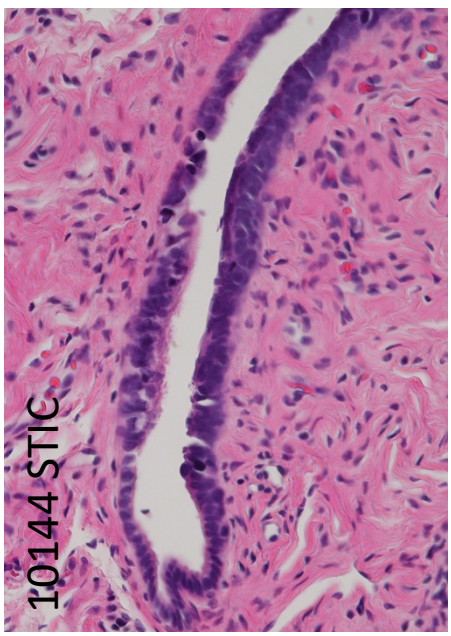
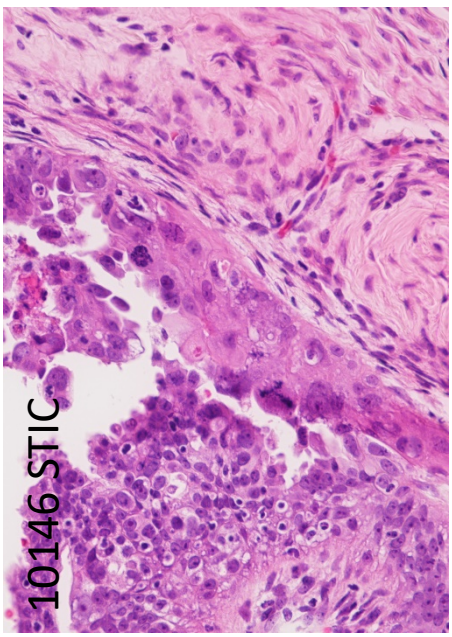

10146 cancer
inflammation


10145 p53 sig


10144 STIC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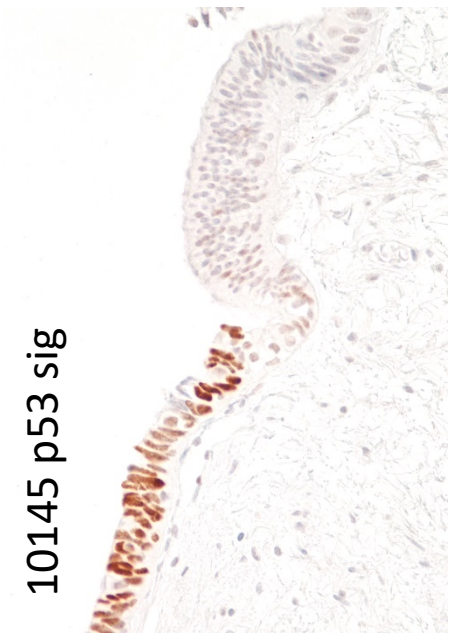
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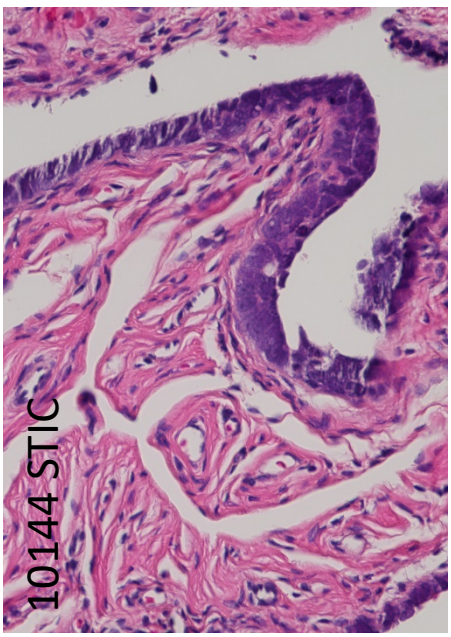
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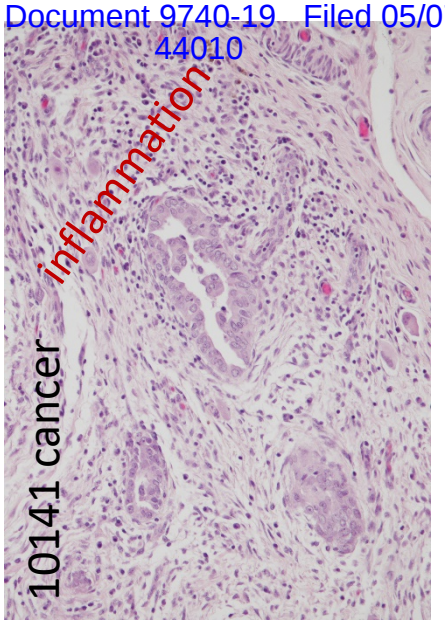
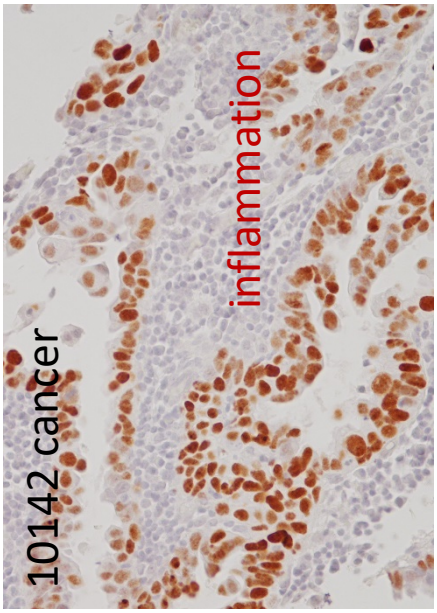

10141 cancer
inflammation


10142 cancer
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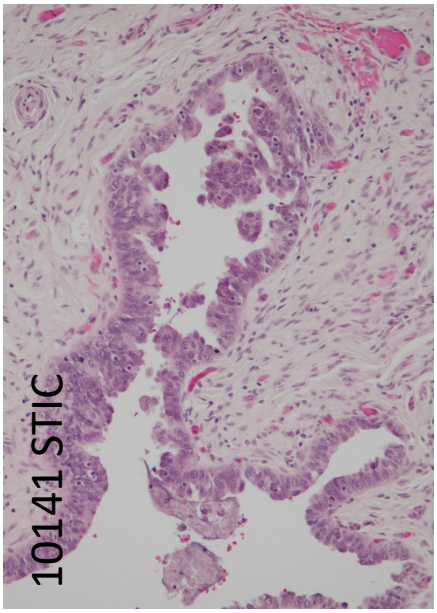
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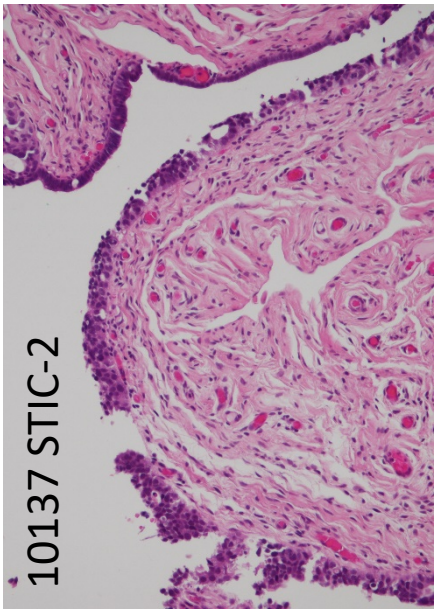
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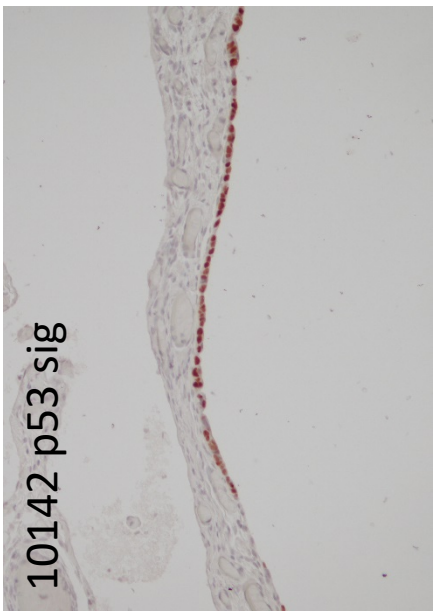
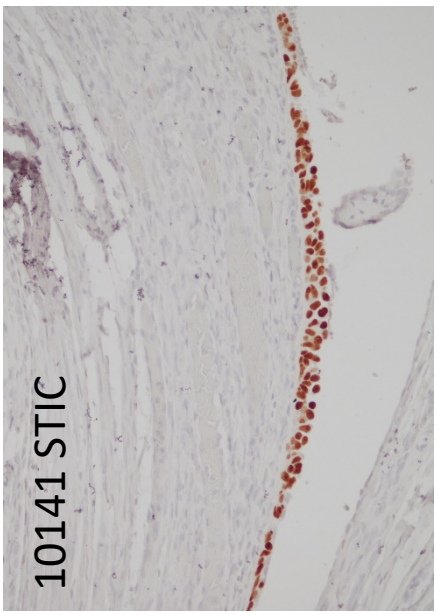

10142 p53 sig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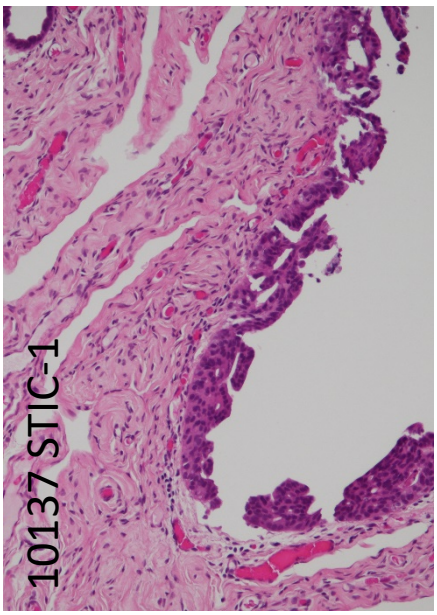
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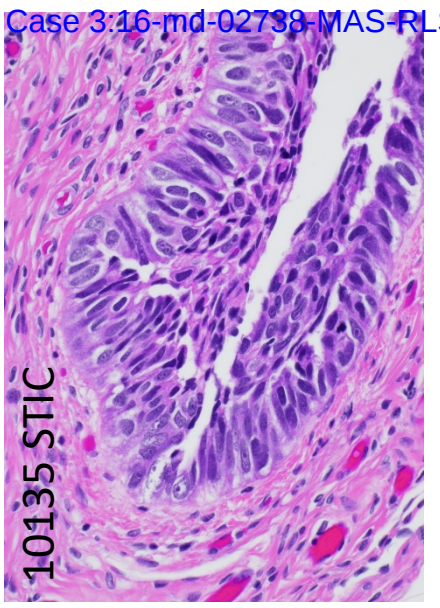
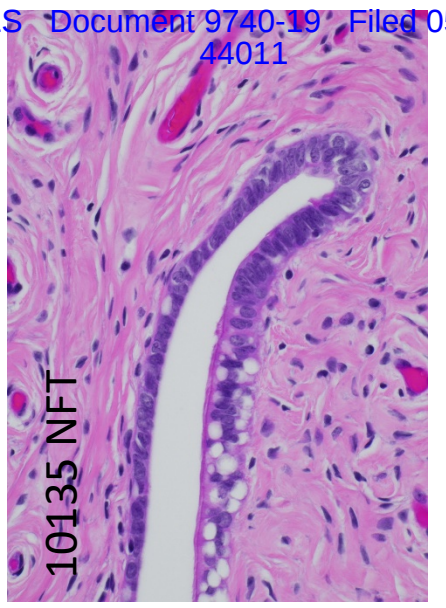

10135 STIC


10135 NFT


10060 STIC
STIC
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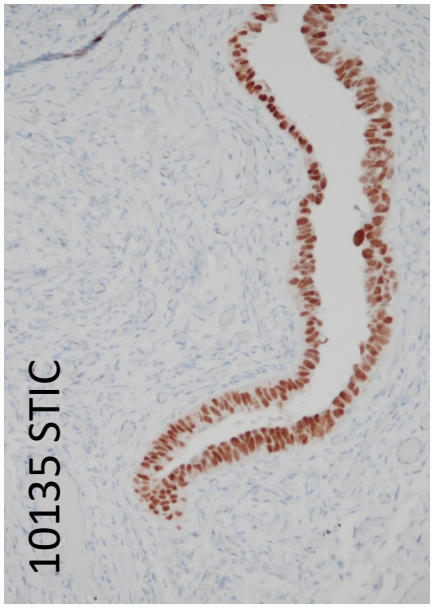
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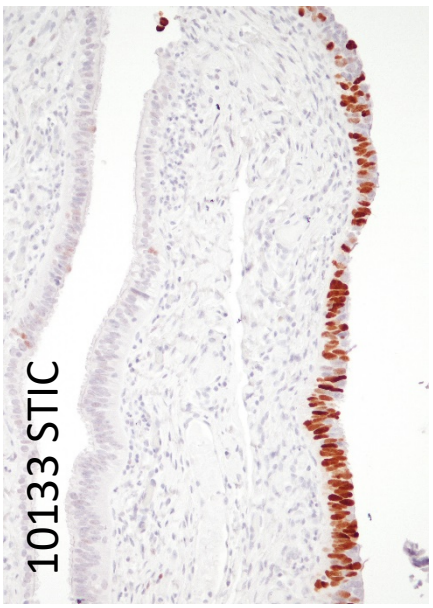
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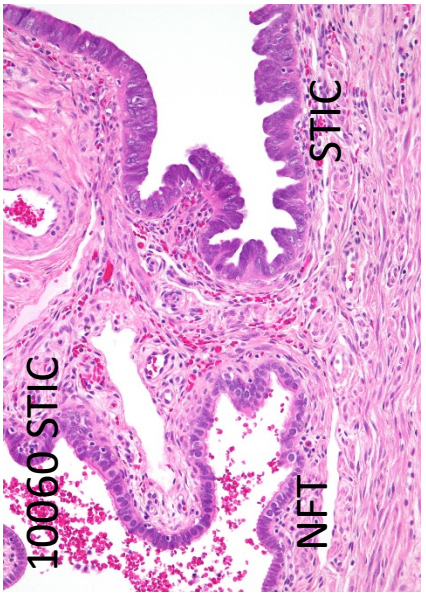
10060 STIC
STIC
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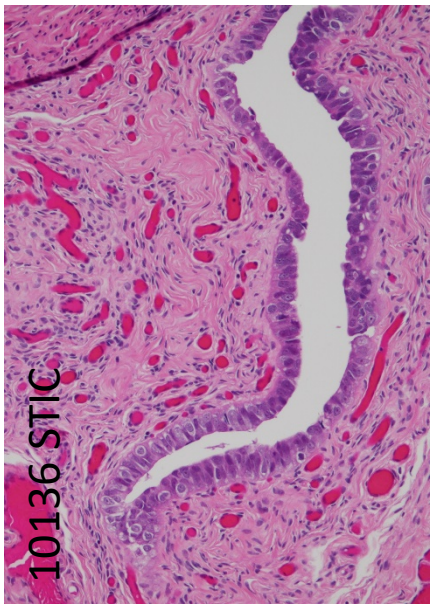
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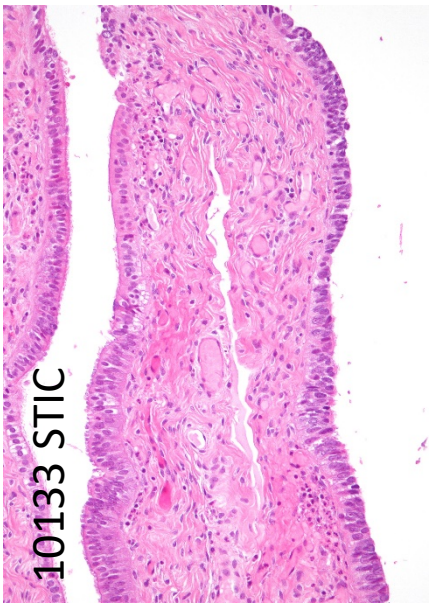
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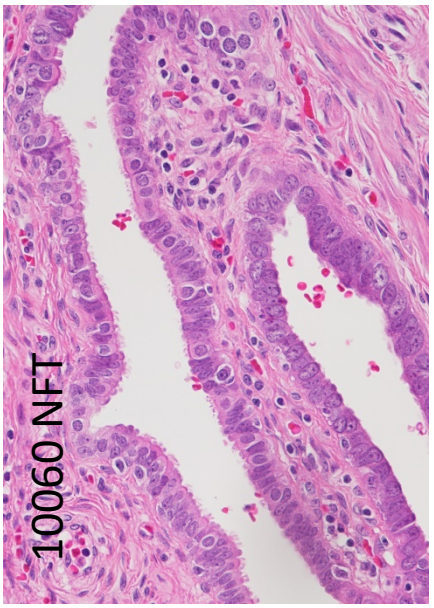
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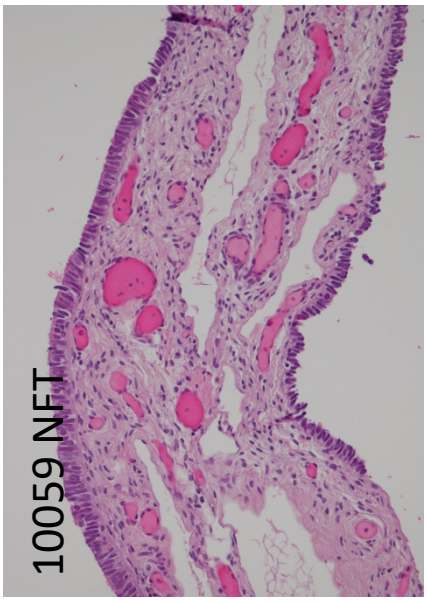
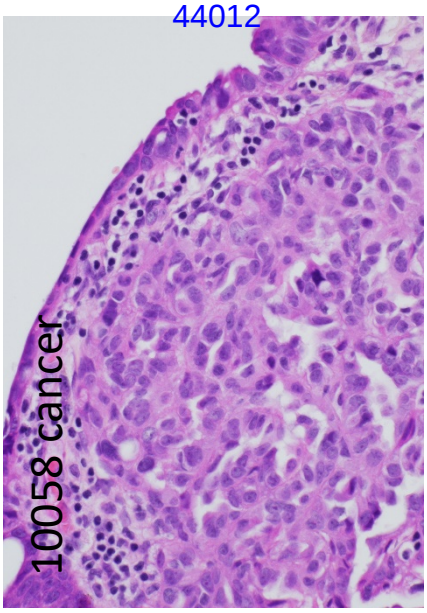
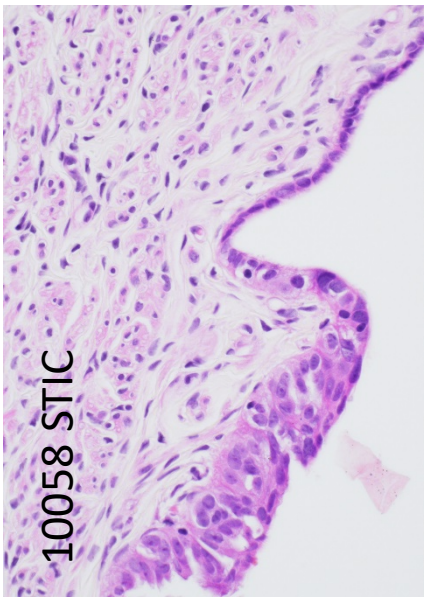
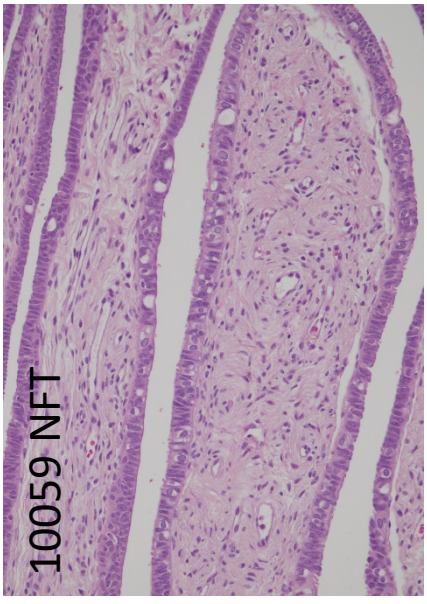

10059 NFT


10058 cancer


10058 STIC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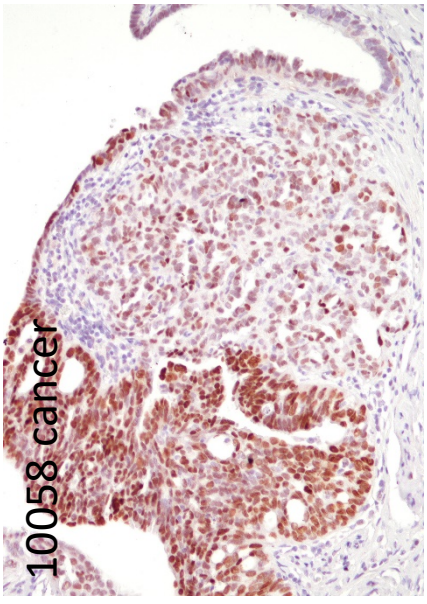
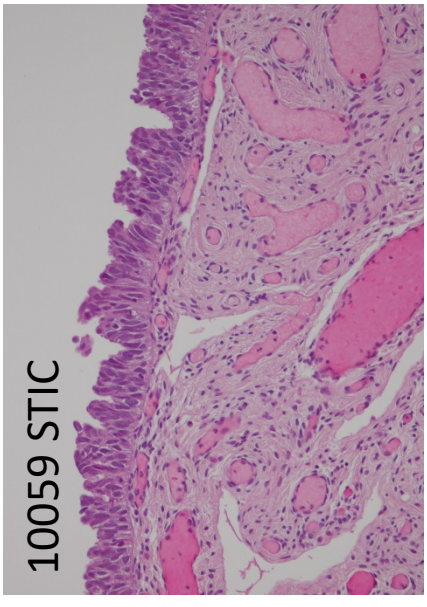

10058 cancer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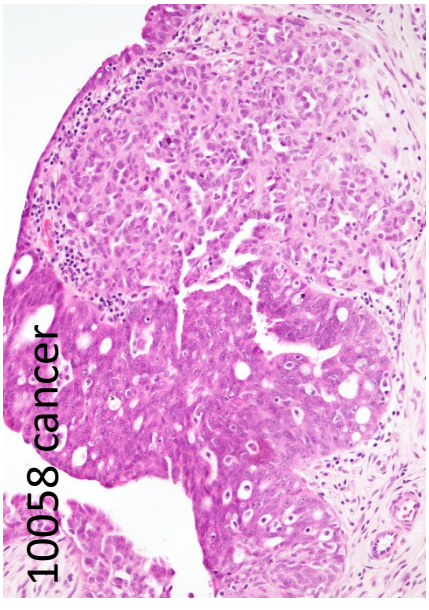
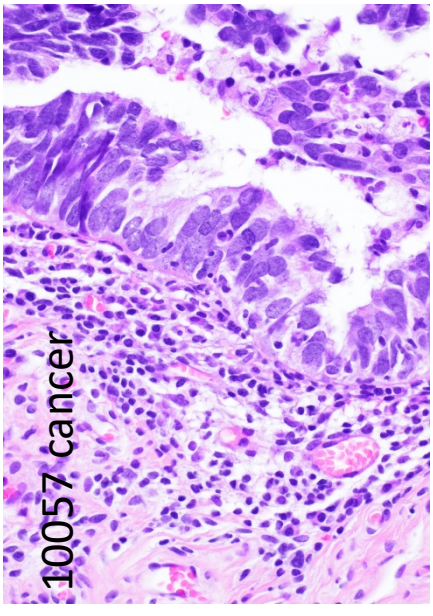
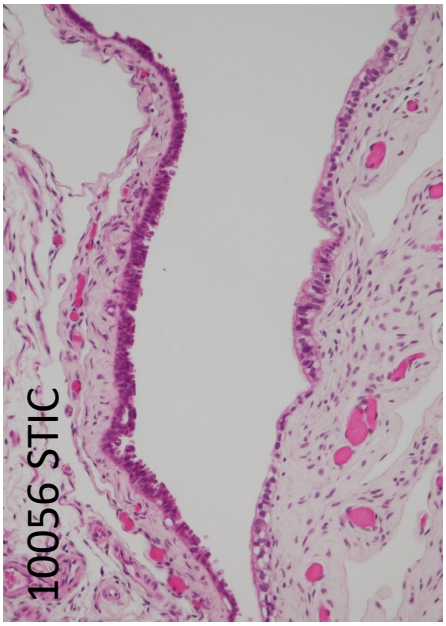
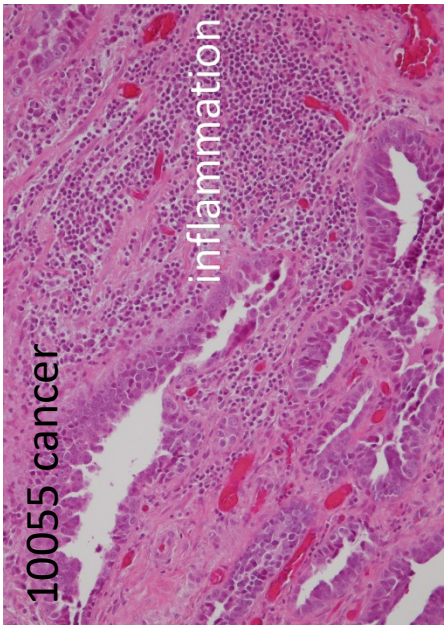
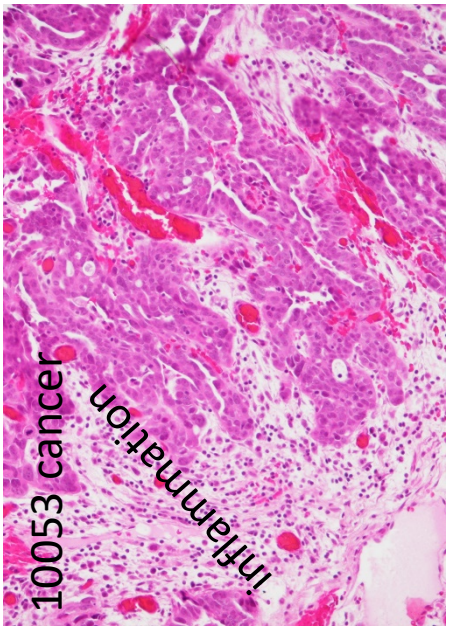
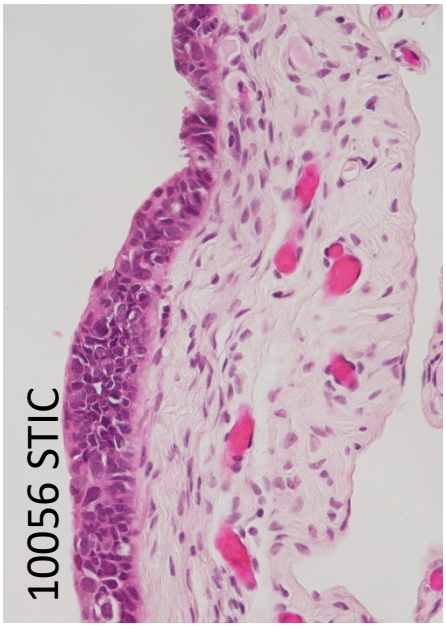

10058 cancer


10057 cancer


10056 STIC


10055 cancer
inflammation


10053 cancer
inflammation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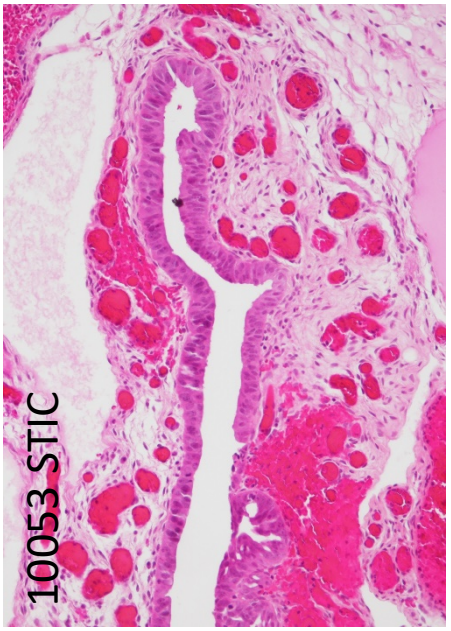
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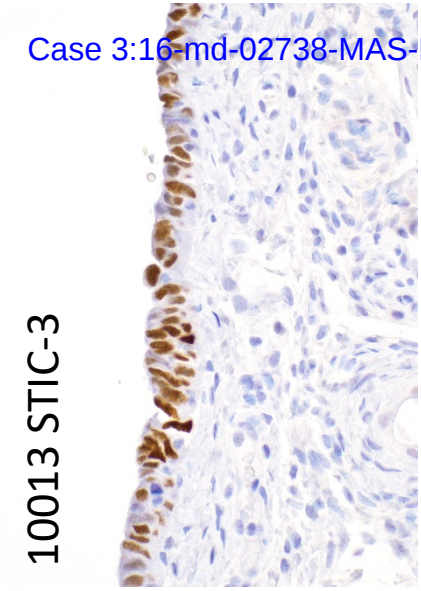
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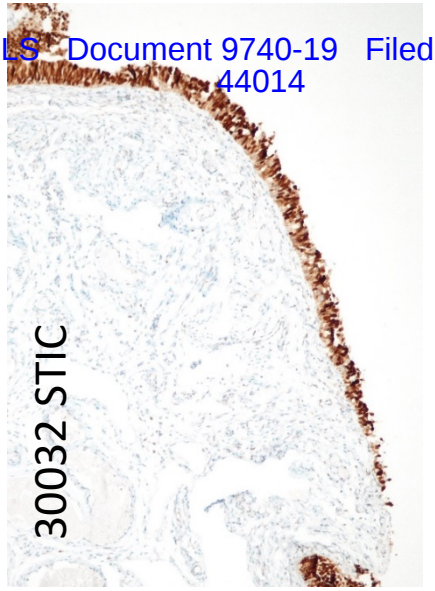
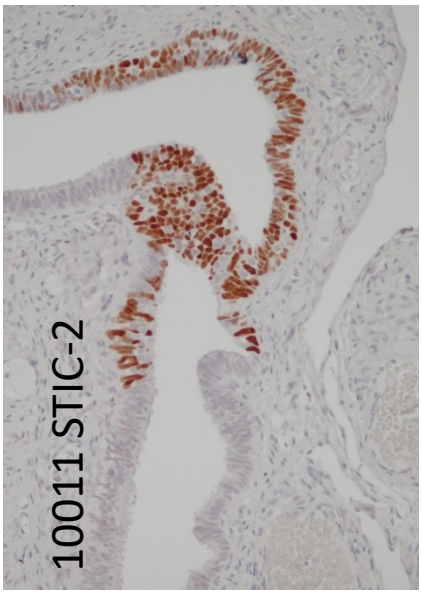
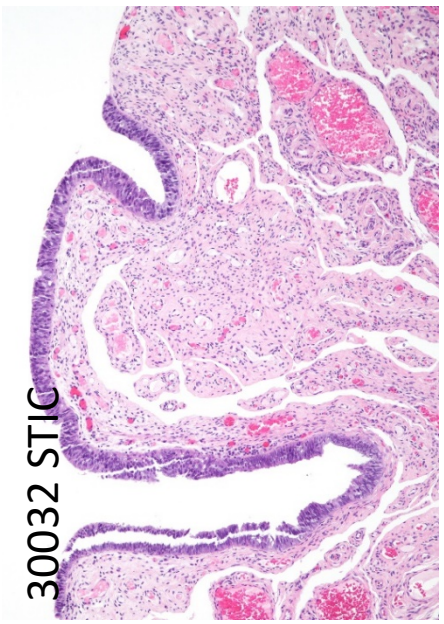
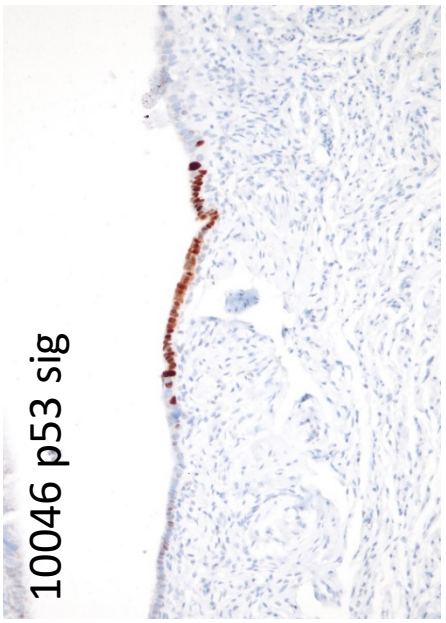
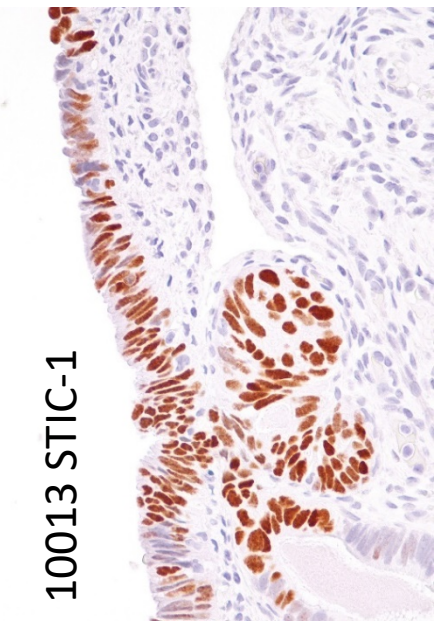

30032 STIC


10011 STIC-2


30032 STIC


10046 p53 sig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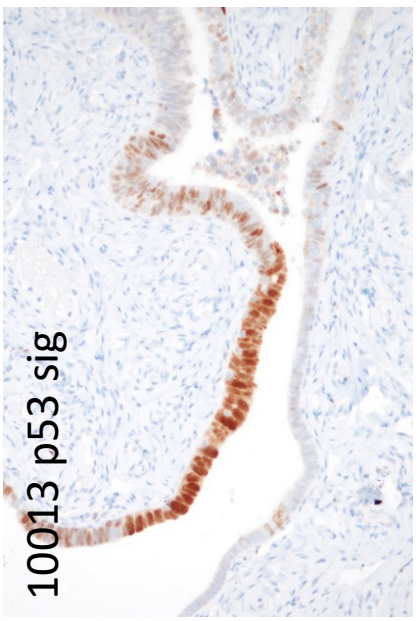
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20073

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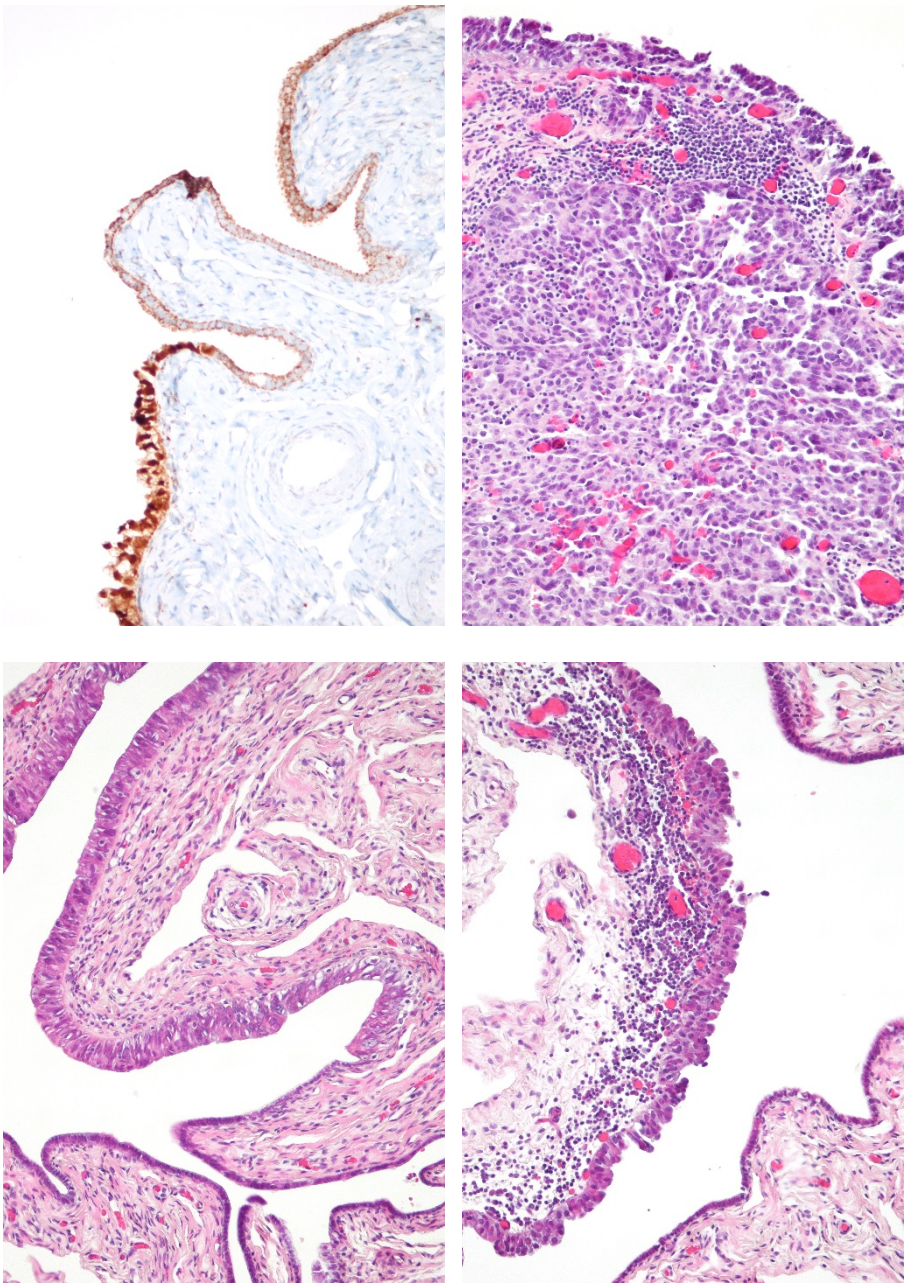

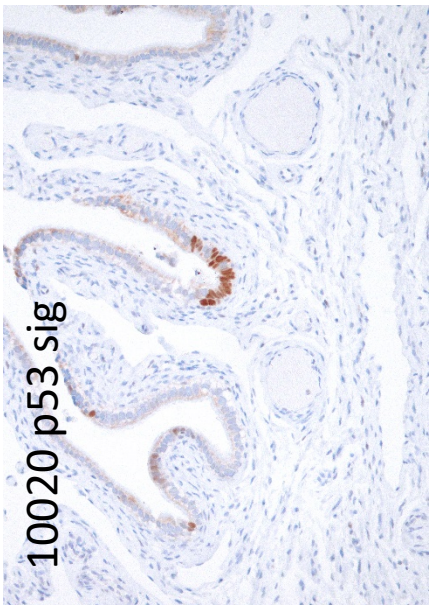
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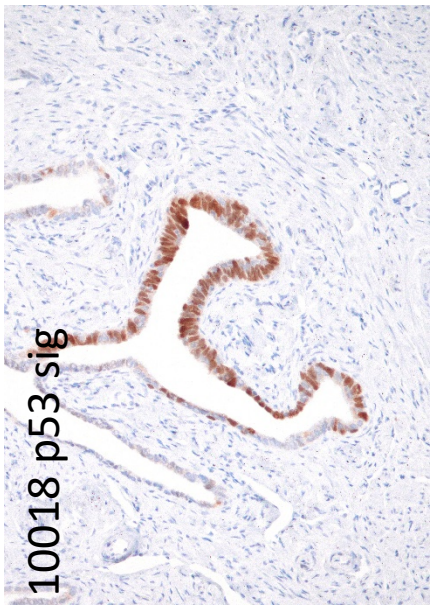
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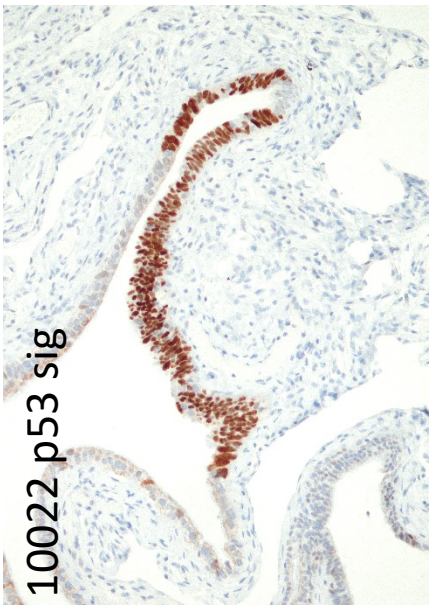
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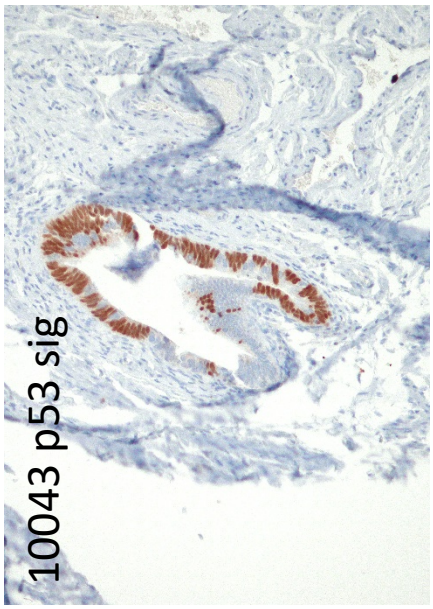
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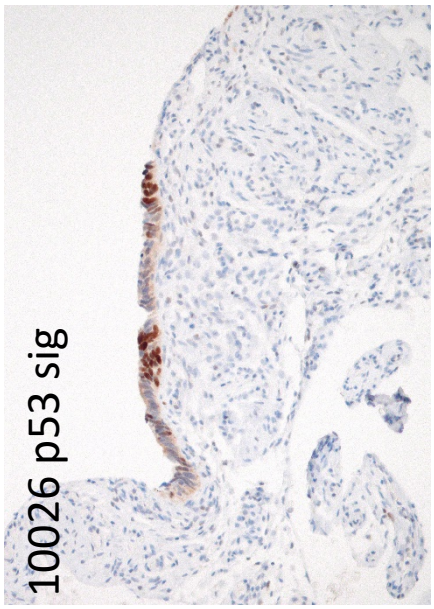
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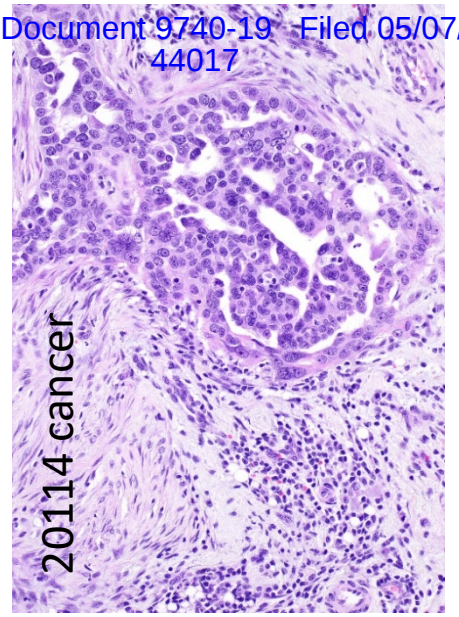
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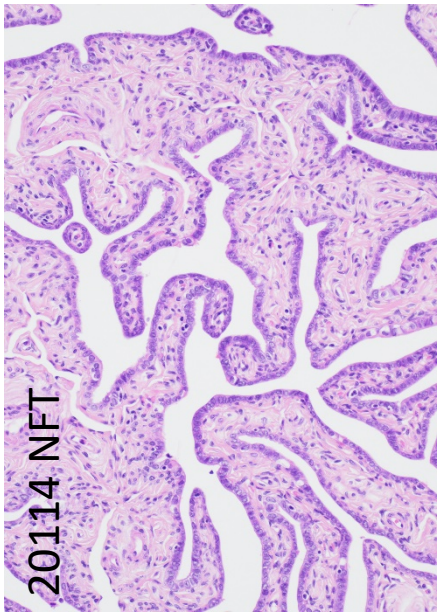
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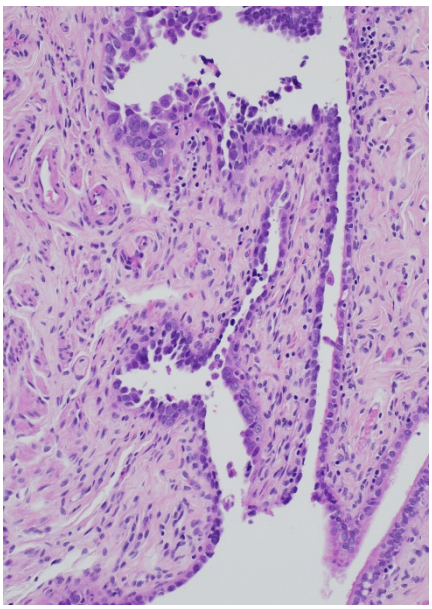

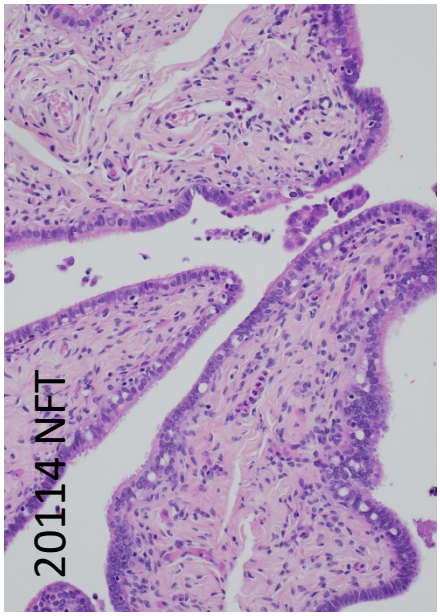
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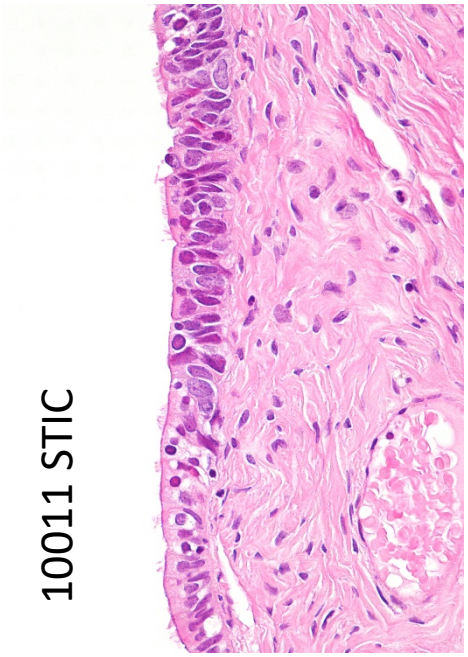
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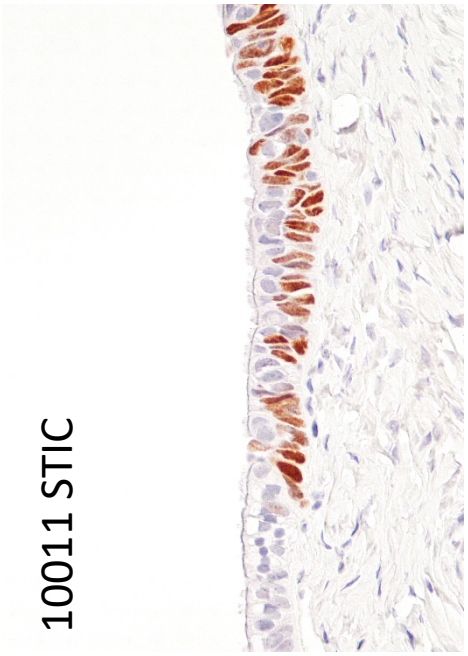
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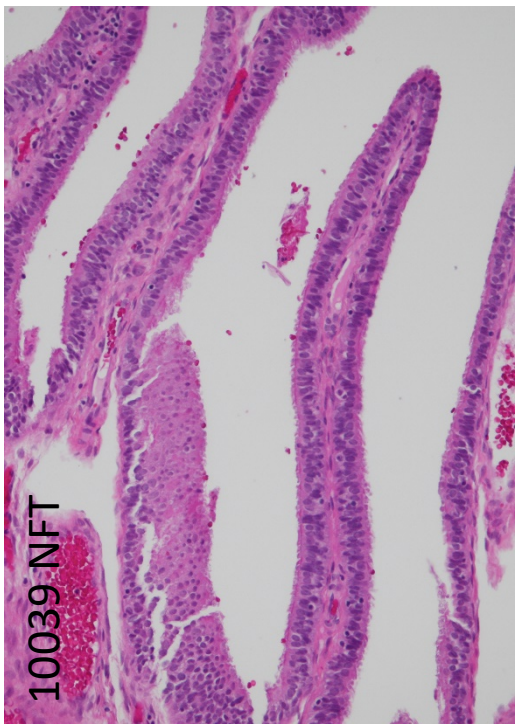
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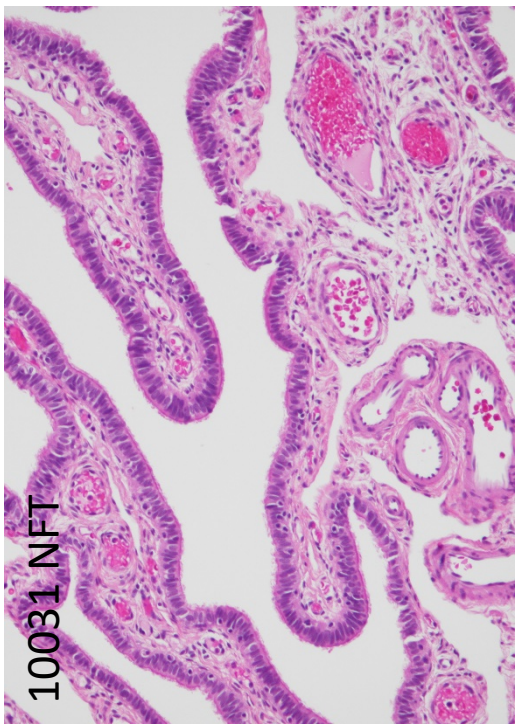
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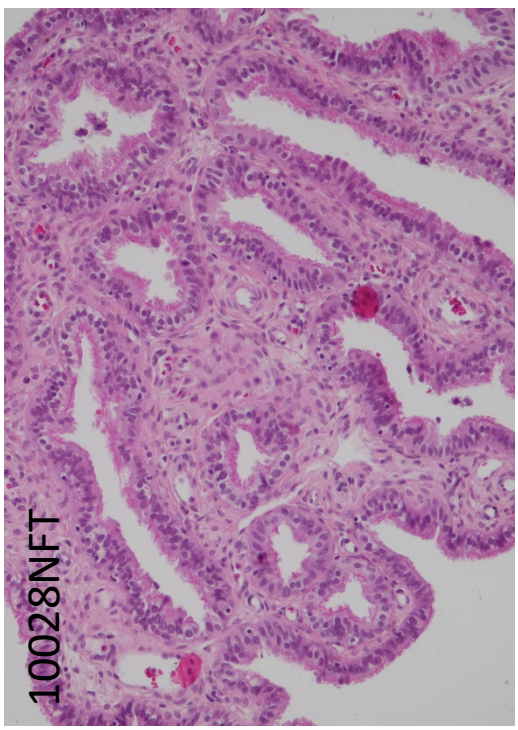
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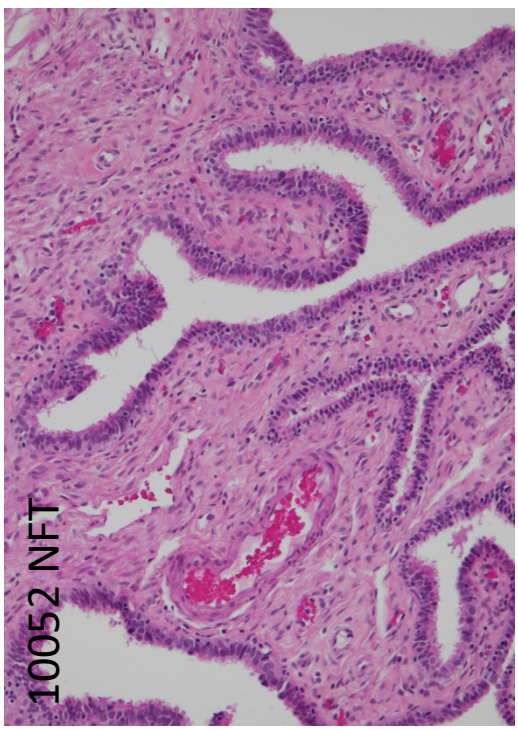
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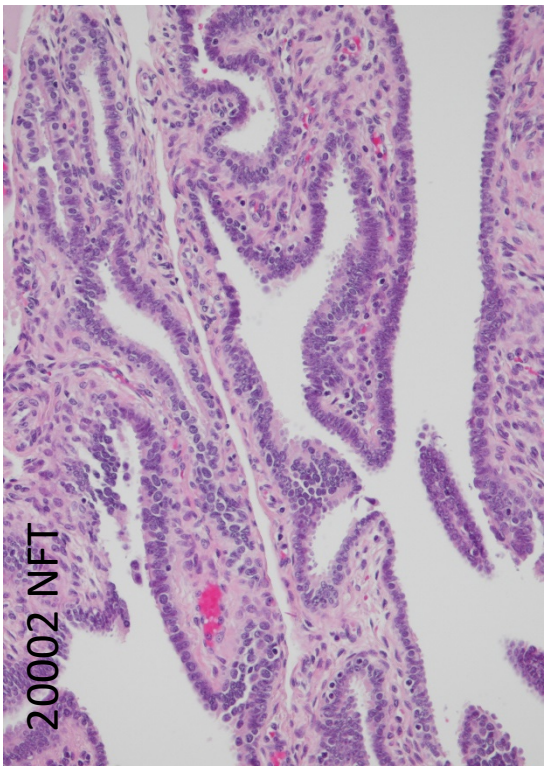
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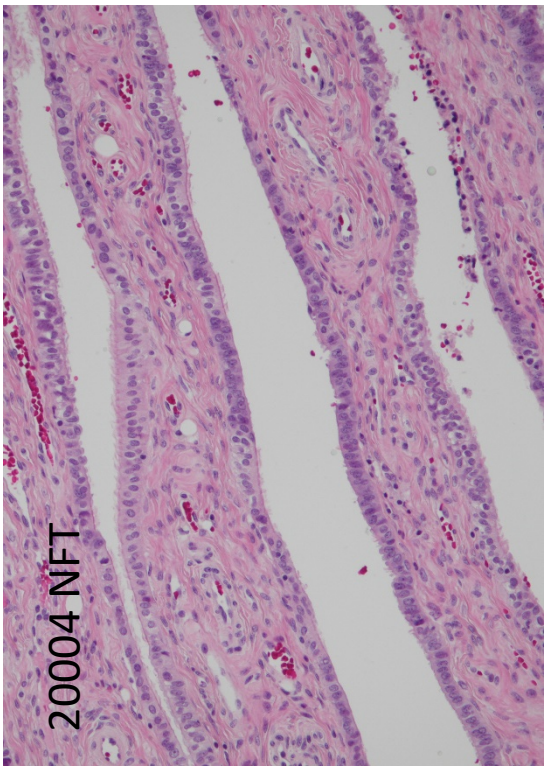
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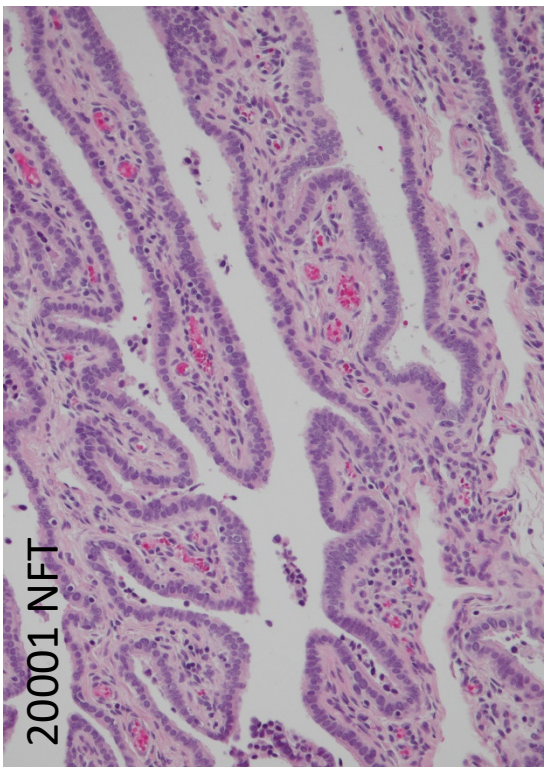
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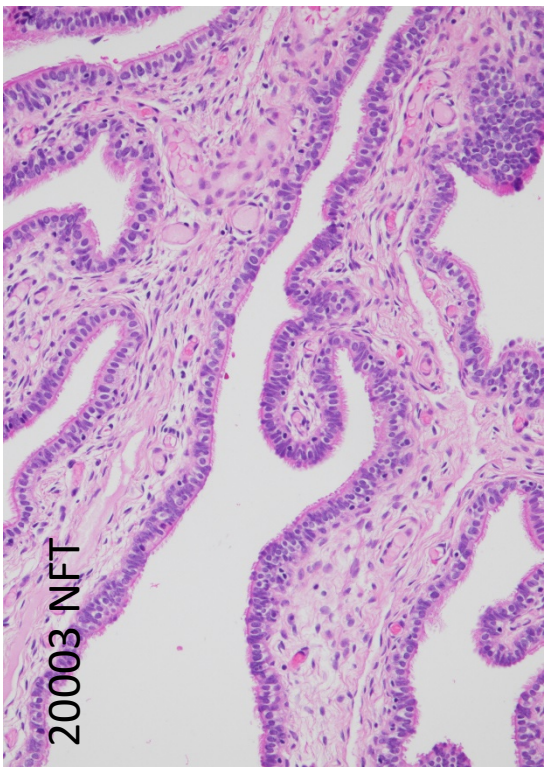
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EXHIBIT A

CURRICULUM VITAE

The Johns Hopkins University School of Medicine

Ie-Ming Shih Version: February 8, 2019

Dr. Ie-Ming Shih is the *Richard W. TeLinde* Distinguished Professor (Endowed Chair) of Gynecologic Pathology (1) and directs this inter-departmental research program at the Johns Hopkins Medical Institutions (2, 3). This endowed professorship with this size is the only one to recognize the academic excellence and authority in the gynecologic pathology field. He also co-directs the *Breast and Ovarian Cancer Program* at the *Sidney Kimmel Comprehensive Cancer Center* at Johns Hopkins. Dr. Shih graduated from the *Taipei Medical University* in 1988 and obtained his Ph.D. from *University of Pennsylvania* in 1993. He is a gynecologic pathologist, trained and board-certified in anatomic pathology, having completed a clinical fellowship in gynecologic pathology followed by a cancer molecular genetics fellowship with Dr. Bert Vogelstein at Hopkins. Since 2000, Dr. Shih has become a faculty member and his research focuses on exploring genomic landscapes and pathogenesis of ovarian and endometrial cancers, developing new target-based therapy and applying innovative technology for early detection of gynecologic cancer. His research team has proposed the new model in classifying ovarian cancer which has become widely used nowadays, helped elucidating the origin of ovarian cancer and develops new technology to detect ovarian cancer. They have also pioneered in elucidating the molecular landscapes in different types of ovarian cancer and identify novel genes and pathways involved in chromatin remodeling, chromosomal instability, cytokinesis and tumor invasion in ovarian cancer. In collaboration with medical and gynecologic oncologists, the research team is initiating new clinical trials that capitalize their new molecular research findings. As an example, they are determining if adding a new kinase inhibitor in the paclitaxel regimen will sensitize chemotherapy in recurrent ovarian cancer. His research is supported by NIH/NCI, DoD and several private foundation awards. Recently, in addition to NIH RO1 and UO1, Dr. Shih has received the NIH award- SPORE (Specialized Program of Research Excellence) of Ovarian Cancer (12.5 million USD for 5 years) as the overall Principal Investigator and led the multi-institutional team for translational ovarian cancer research including the development of early detection and novel therapies. The inter-departmental TeLinde Gynecologic Pathology Research program he is leading has generated more than 6.6 million USD/yr in research funding in 2018. Dr. Shih has published more than 350 original articles and book chapters in prestigious journals such as *New England Journal of Medicine*, *Cancer Cell*, *Journal of National Cancer Institute*, *PNAS*, *Science, Lancet Oncology, Nature* and *Nature Medicine*, etc. which have been cited over 33,000 times. He has been invited to give more than 110 lectures worldwide. Dr. Shih is also a devoted teacher who has helped career development of many young scientists and physicians to pursue academic career and excellence. He sits on several advisory boards such as NCI Ovarian Task Force of Gynecologic Cancer Steering Committee and Ovarian Cancer Research Foundation, etc. and serves as an editorial board member in Cancer Research, Journal of Pathology, American Journal of Pathology and several others. Besides his clinical, research, and teaching obligations, he is also a passionate photographer (4).

1. https://professorships.jhu.edu/professorship/richard-w-telinde-distinguished-professorship-in-gynecological-pathology/
2. www.hopkinsmedicine.org/gynecology_obstetrics/research/areas/telinde_lab.html
3. www.gynecologycancer.org
4. www.shih-photography.com

DEMOGRAPHIC AND PERSONAL INFORMATION

Current Appointments

Richard W. TeLinde Distinguished Professor, Department of Gynecology and Obstetrics with secondary appointment in the Departments of Oncology and Pathology, Johns Hopkins Medical Institutions

Co-Director, the Breast and Ovarian Cancer Program, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Medical Institutions

Personal Data

Country of birth place: Dai-Chia Township, Tai-Chuan City, Taiwan
Nationality/citizenship: 1) United States of America; 2) Taiwan
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Fax: 410-502-7943
E-mail: ishih@jhmi.edu, shihie@yahoo.com

EDUCATION AND TRAINING

Year	Degree	Institution	Discipline
1981-1988	M.D.	Taipei Medical University	Medicine
1989- 1993	Ph.D.	University of Pennsylvania	Biomedical Science (pathology)
1993-1994	Postdoctoral Fellow	The Wistar Institute	Cancer Biology
1994-1997	Resident	Johns Hopkins Hospital	Pathology
1997-1998	Clinical Fellow	Johns Hopkins Hospital	Gynecologic Pathology
1998-2000	Research Fellow	Johns Hopkins Oncology Ctr. (w/ Dr. Bert Vogelstein)	Cancer Genetics

PROFESSIONAL EXPERIENCE

2000-2001 **Instructor**, Department of Pathology
Johns Hopkins Medical Institutions, Baltimore, MD

2001-2003 **Assistant Professor**, Department of Pathology
Johns Hopkins Medical Institutions, Baltimore, MD

2003-2008 **Associate Professor**, Departments of Pathology, Oncology and Gynecology and Obstetrics

Johns Hopkins Medical Institutions, Baltimore, MD

2008- **Professor**, Departments of Pathology, Oncology and Gynecology/Obstetrics
Johns Hopkins Medical Institutions, Baltimore, MD

2014- **Richard W. TeLinde Distinguished Professor (endowed Chair)**
http://webapps.jhu.edu/namedprofessorships/professorshipdetail.cfm?professorshipID=220
Department of Gynecology and Obstetrics
Johns Hopkins University School of Medicine

Director of Johns Hopkins TeLinde Gynecologic Pathology Research Program
http://www.hopkinsmedicine.org/gynecology_obstetrics/research/areas/telinde_lab.htm
Department of Gynecology and Obstetrics
Johns Hopkins University School of Medicine

Co-director of the Breast and Ovarian Cancer Program,
Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Medical Institutions, Baltimore, MD

RESEARCH ACTIVITIES

research website: www.gynecologycancer.org

Peer-Reviewed Research Articles

Dr. Shih's publications can be found in NCBI *My Bibliography* at:
https://www.ncbi.nlm.nih.gov/myncbi/collections/bibliography/47955017/

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2. Valyi-Nagy I, **Shih IM**, Gyorfi T, Greenstein D, Elder DE, Herlyn M. Spontaneous and induced differentiation of cultured human melanoma cells. Int J Cancer, 54:159-165, 1993. PMID: 8478142

3. Valyi-Nagy I, Hirka G, Jensen PJ, **Shih IM**, Juhasz I, Herlyn M. Undifferentiated keratinocytes control growth, morphology, and antigen expression of normal melanocytes through cell-cell contact. Lab Invest, 69:152-159, 1993. PMID: 8350597

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Inventions, Patents, Copyrights

- US patent #6419896: Non-invasive approach for assessing tumor in living animals. Inventors: Vogelstein B, Kinzler WK and Shih I-M
- US patent #20110171741: DNA integrity assay (DIA) for cancer diagnostics, using confocal fluorescence spectroscopy. Inventors: Tza-Hui Wang, Kelvin J. Liu, Ie-Ming Shih
- US patent in process (11/604,183): Application of Rsf-1 expression to predict clinical outcome in cancer patients. Inventors: Shih I-M and Wang T-L
- International patent in progress (PCT/US2008/011948): Detection of cancer by measuring genomic DNA copy number and strand length in cell-free DNA. Inventors: Shih I-M

Extramural Funding

Current awarded Grants

04/01/17 - 03/30/22	Experimental Therapeutics by targeting Spleen Tyrosine Kinase RO1 CA215483 NCI/NIH Role: PI Purpose: The goal is to elucidate the molecular mechanism how SYK enhances paclitaxel resistance through modulating microtubule dynamics and identify the potential biomarker for outcome prediction
4/1/2016 – 3/31/2021	Early Detection Research Network (EDRN) UO1 CA200469 Development of in vitro diagnostic multivariate index assay using liquid-based cervical cytology specimen and/or serum/plasma biomarkers for the detection of early stage or low-volume ovarian cancer NCI/NIH Role: Principal Investigator (multiple PIs: Shih & Zhang) Purpose: To identify protein biomarkers and develop immunoassays for ovarian cancer detection in liquid-based cervical cytologic samples and blood.
07/01/2018-6/30/2023	SPORE (Specialized Programs of Research Excellence) in Ovarian Cancer P50 CA228991-01 NIH/NCI Role: Principal Investigator (overall) Purpose: The program consists of four research projects, three cores and two programs to promote translational research including early phase clinical trials in ovarian cancer.
01/01/2017-12/31/2020	Development of Targeted Therapies for Recurrent Ovarian Cancer Collaborative Research Development Grant # 458972 Ovarian Cancer Research Foundation Alliance (OCRFA) Role: PI Purpose: Development of a research program which focuses on identifying and characterizing promising new anti-tumor molecules and develop/apply inhibitors for targeted therapy in ovarian cancer
01/15/2017 – 01/14/2020	Development of early detection molecular platform for ovarian cancer in high-risk women Grant contract (PIs: I-M Shih and A Fader) Gray Foundation Role: co-PI Purpose: This study focuses on applying sequencing technology to detect ovarian cancer associated mutations in liquid-based cytology specimens in women with increased risk of ovarian cancer.

01/03/2017 – 2/28/2020	Molecular study on endometriosis Endometriosis Foundation of America Role: PI Purpose: Applying next-generation sequencing to elucidate the somatic mutations in deeply infiltrative endometriosis
01/01/2018- 12/31/2021	Integration of advanced genomic and bioengineering approaches for early detection and prevention of ovarian cancer. Tina Brozman Foundation Consortium Grant Role: co-PI Purpose: Identify and characterize molecular biomarkers of fallopian tube lesions which are the precursors of high-grade ovarian serous carcinoma
11/01/2016- 10/31/2020	PapDREAMing for early detection of ovarian cancer. Tina Brozman Foundation Consortium Grant Role: PI Purpose: Identify a panel of methylation biomarkers and develop a methylation-based assay to detect ovarian cancer using liquid cervical cytology specimens

Recent Completed Research Grants

10/01/2011 – 06/30/2018	Prevention of Ovarian High-Grade Serous Carcinoma by Elucidating Its Early Changes, W81XWH-11-2-0230 OC100517 (Director: RJ Kurman; co-Director: I-M Shih) Consortium Award, US Department of Defense (USAMRMC), Directed Medical Research Programs (CDMRP) Role: Co-director and co-investigator; 3.0 calendar months Purpose: To determine the origin and pathogenesis in the development of ovarian high-grade serous carcinomas by employing cancer genetics, cell biology, animal models and epidemiologic studies through multi-institutional research effort. The consortium includes five research projects and three cores.
09/01/2011 - 08/30/2016	Proteome characterization center: a genoproteomics pipeline for cancer biomarker. Clinical Proteomic Technologies for Cancer Initiative. U24CA160036 (PI: D Chan) NCI/NIH Role: co-investigator; 1.0 calendar months Purpose: To identify, verify and characterize biomarkers for ovarian cancer by combining genomics and proteomic approaches. To establish the clinical proteomic technology center and to validate, verify and characterized of ovarian cancer biomarkers using genoproteomic approaches.
4/1/2011 – 3/31/2017	Notch3 signaling in ovarian cancer

	RO1 CA148826 (PI: TL Wang) NCI/NIH Role: co-investigator; 0.5 calendar months Purpose: To investigate the molecular mechanism of Notch3 signaling in the pathogenesis of ovarian high-grade serous carcinoma.
12/01/2004 - 11/30/2012	Molecular Diagnostics for Malignant Effusion 2R01 CA103937 (PI: I-M Shih) NCI/NIH Role: principal investigator; 1.0 calendar months Purpose: To study the functional role of NAC-1 in the development of ovarian carcinoma.
4/01/2008 - 1/31/2013	The Roles of HBXAP Gene in Ovarian Cancer 1R01 CA129080 (PI: I-M Shih) NCI/NIH Role: principal investigator; 1.0 calendar months Purpose: To study the molecular mechanism of HBXAP gene product in the progression of ovarian carcinoma.
07/01/2011 - 06/30/2016	Multiplexed Detection of Cell Free DNA Biomarkers for Cancer RO1 CA155305 (PI: TZ Wang) NCI/NIH Role: co-investigator; 1.0 calendar months Purpose: To analyze the potential application of multiplexed detection of cell free DNA as biomarkers for cancer detection.
04/01/2007 - 01/31/2012	Pathogenesis of Ovarian Serous Borderline Tumors RO1 CA116184 (PI: R.J. Kurman) NCI/NIH Role: co-Director, project 1 leader; 0.5 calendar months Purpose: To study the molecular genetic profiles of implants that is associated with ovarian serous borderline tumors. To develop biomarkers to better diagnose the implant and correlate the molecular genetic profiles and biomarker expression with clinical behavior in patients.
07/01/2002- 06/30/2007	Development of a New Technology in Analyzing Allelic Imbalance in Plasma DNA as a Tool for Early Cancer Detection R21/R33 CA97527 (PI: Shih) NCI/NIH Role: principal investigator; 4.0 calendar months Purpose: To develop an innovative molecular method to better diagnose human cancer using cell-free circulating DNA in patients.
09/30/2014-09/29/2016	Targeting the Mevalonate Pathway to Reduce Mortality from Ovarian Cancer DoD W81XWH-14-10021 DoD, OCRP Role: co-investigator

	Purpose: To determine if targeting the mevalonate pathway in ovarian cancer has biological and pre-clinical utility in delaying tumor progression in ovarian high-grade serous carcinoma. Several cell biology and molecular biologic approaches together with animal ovarian tumor models will be applied.
07/01/2008 - 06/30/2012	Notch3 Signaling Pathway in the Ovarian Carcinoma GMC-113937 (PI: TL Wang) American Cancer Society Role: co-investigator; 1.0 calendar month Purpose: This project is to characterize the role of Notch3 signaling pathway in ovarian tumorigenesis and identify Notch3 down-stream target genes in ovarian cancer.
06/01/2009 – 05/31/2012	High-throughput intracellular microrheology: a new tool for cancer research 1R21CA137686 (PI: D Wirtz/IM Shih) NCI/NIH Role: Co-PI Purpose: To apply a high-throughput intracellular microrheology in studying ovarian cancer
12/01/2011 - 11/30/2014	Tumor suppressor role of ARID1A R21 CA165807 (PI: IM Shih) NCI/NIH Role: principal investigator; 1.0 calendar months Purpose: To determine the tumor suppressor roles of ARID1A and its molecular mechanisms in developing gynecological cancer.
07/01/2002- 06/30/2006	Diverse Pathways in the Development of Ovarian Serous Tumors OC010017 (PI: RJ Kurman) US Department of Defense (USAMRMC), Directed Medical Research Programs (CDMRP) Role: Project #1 leader; 3.0 calendar months Purpose: To study the molecular pathways that is involved in the development of different types of ovarian serous carcinoma by using several new technologies including SAGE.
09/01/2003- 08/30/2004	Molecular genetic changes in the development of cervical cancer P50CA098252- SPORE (PI: TC Wu) NIH/NCI Role: co-investigator; 1.0 calendar month Purpose: The development project/pilot study in this SPORE of cervical cancer is to investigate the DNA copy number changes involved in the development of cervical cancer.
12/28/2005- 12/27/2006	Marker Discovery for Ovarian Cancer Research agreement Developmental Center of Biotechnology, Taiwan (PI: Shih) Role: principal investigator; 1.0 calendar month

	Purpose: To identify biomarkers for potential use in ovarian cancer diagnosis and therapy.
10/01/2006 - 09/30/2007	Characterization of Rsf-1 in human cancer China Medical University, Taiwan Research agreement (PI: Shih) Role: principal investigator; no salary requested Purpose: To study the molecular etiology of Rsf-1 expression in oral cancer in Taiwanese patients.
1/1/2008 - 12/31/2009	Notch3 signaling in the pathogenesis of ovarian cancer Ovarian Cancer Research Foundation (OCRF, New York) Individual Investigator Award (PI: T.L. Wang) Role: co-investigator; 0.6 calendar month Purpose: To characterize the Notch3 signaling pathway in the tumor progression of ovarian cancer. Specifically, the proposal is to determine how the Notch3 pathway goes awry in normal ovaries and the molecular mechanisms in which Notch3 pathway aberration contributes to ovarian cancer.
01/01/2009 – 12/31/2010	Screening of Chinese herbal medicine extracts in cancer therapy Research Agreement (PI: IM Shih) China Medical University, Taichung city, Taiwan Role: Principal; investigator Purpose: To screen candidate Chinese herbal extracts to inhibit specific cancer-associated targets for potential molecularly targeted therapy.
12/11/2006 - 12/31/2007	Molecular Markers for Clinical Outcome Prediction Oncotech, Inc. Research Agreement (PI: Shih) Role: principal investigator; 0.60 calendar month Purpose: To assess the clinical potential of Rsf-1 and NAC-1 immunohistochemistry in predicting clinical outcome in ovarian cancer patients.
04/01/2008 - 03/31/2010	Nanobiosensing Method for Point Mutation Detection of Cancer 1R21CA120742 (PI: TZ Wang) NCI/NIH Role: co-investigator; 0.60 calendar month Purpose: To develop a nanobiosensing technical platform to detect point sequence mutation of Kras and Braf genes using a relatively small amount of DNA samples without PCR.
07/01/2007 - 06/31/2009	Characterization of Chromatin Remodeling Gene, Rsf-1, in Pathogenesis of Ovarian Cancer Johns Hopkins-Weizmann Inst. (PI: Shih) Role: principal investigator; 0.60 calendar month Purpose: To study the biological function of Rsf-1 gene in the development of ovarian cancer.

01/01/2005 -12/31/2008	Identification and Characterization of Genomic Amplifications in Ovarian Serous Carcinoma OC04-0060 (PI: T.L. Wang) US Department of Defense (USAMRMC), Directed Medical Research Programs (CDMRP), New Investigator Research award Role: co-investigator; 1.0 calendar month Purpose: To identify and characterize ovarian cancer genome using digital karyotyping and SNP array.
07/01/2009 – 06/30/2011	Elucidation of molecular alterations in precursor lesions of ovarian serous carcinoma OC080469 (Director: RJ Kurman; Co-director: IM Shih) Role: Co-director Purpose: To establish ovarian cancer research consortiums to facilitate identify and characterize early lesions of ovarian cancer through multiple institution collaborations

EDUCATIONAL ACTIVITIES

Classroom Instruction (Johns Hopkins University School of Medicine)

- Gynecological Pathology and laboratory/small group, Pathology course for medical students, 1994-
- Graduate course in Pathobiology and Disease Mechanisms, Section of Ovarian Tumors, 2002-
- Graduate course in Functional Anatomy ("Female Reproductive Organ"), for graduate students, Johns Hopkins University, 2006-
- Graduate course in Pathobiology ("Gynecological Pathology") for graduate students, Johns Hopkins University, 2005-

Clinical Instruction (the Johns Hopkins Hospital)

- Microscopic and gross teachings for medical students, residents and fellows rotating to gynecologic pathology, 1999-
- Didactic course on Gynecologic Pathology for residents and fellows, 2002-

CME course speaker

- "Molecular pathways of ovarian cancer". At the Current Concepts in the Multidisciplinary Management of Ovarian Cancer, the Sidney Kimmel Cancer Center and the office of Continuing Medical Education, Johns Hopkins University, Baltimore, September, 2004.
- "Molecular genetics and target-based therapy for low-grade serous cancers of the ovary". At the Current Concepts in the Multidisciplinary Management of Ovarian Cancer, the office of Continuing Medical Education, Johns Hopkins University, Baltimore, September, 2005.
- "Gynecologic neoplasms- trophoblastic tumors and ovarian epithelial neoplasms". Symposium of the Taiwanese Association of Pathology, August 2006.
- "Update in gestational trophoblastic disease". Surgical Pathology Update, Leipzig, Germany, June, 2007.

Mentoring

Research Fellows

- 2000-2002, Hsueh-Wei Chang, PhD, currently Chairman and Professor of the Department of Biological Science and Environmental Biology, Kaohsiung Medical University, Taiwan
- 2001-2003, Gad Singer, M.D., Professor at the Institute of Pathology, Baden, Switzerland
- 2002-2004, Brant G. Wang, MD, PhD, research fellow; currently an attending pathologist at the Washington Medical Center, Washington DC
- 2003-2004, Gudrun Pohl, MD, assistant professor at the University of Vienna, Austria
- 2003-2004, Chung-Liang Ho, MD, PhD, Associate Professor, National Chenug-Kung University School of Medicine, Tainan, Taiwan
- 2003, Ariane Aigelsreiter, MD, visiting research fellow, Austria
- 2003-2004, Reiko Dehari, MD, Visiting research fellow, Japan
- 2003-2004, Chih-Yi Hsu, MD, Visiting research fellow, currently a faculty t the National Yang-Ming University School of Medicine/VGH -Taipei, Taiwan
- 2004-2005, Tsung-Hsuan Lai, MD, Director of Reproductive Endocrinology and Infertility division, Department of Ob and Gyn, Taipei Cathay General Hospital, Taipei, Taiwan
- 2004-2006, Kentaro Nakayma, MD, PhD, Associate Professor, Shimane National University School of Medicine, Japan
- 2005-2007, Jim Sheu, PhD, Professor at the Institute of Biomedical Sciences, National Sun Yat-Sen University, Taiwan
- 2005-2006, Ritu Salani, MD, Assoicate Professor and attending physician at the Ohio State University Health System, division of Gynecologic Oncology
- 2007 – current (visiting scholar), Ayse Ayhan, MD, PhD, attending/consulting pathologist at the Seirei Mikatahara General Hospital, Hamamatsu, Japan
- 2005-2007, Tsui-Lien Mao, MD, research fellow, currently an Associate Professor at the National Taiwan University College of Medicine, Taipei, Taiwan
- 2007, Artit Jinawath, MD, PhD, research fellow/visiting resident, Thailand
- 2006-2008, Natini, Jinawath, MD, PhD, research fellow, currently an Assistant Professor at Mahidol University, Thailand
- 2006-2008, Jung Hye Choi, PhD, Associate Professor at Life and Nanopharmaceutical Science, College of Pharmacy, Kyung Hee University, Seoul, South Korea
- 2006-2008, Kuan-Ting Kuo, MD, Associate Professor at the National Taiwan University Hospital, Taipei, Taiwan
- 2007-2008, Stefanie Ueda, MD, Assistant Profession, Department of Obstetrics and Gynecology, University of California at San Francisco, CA
- 2008-2010, Michelle Thiaville, PhD, Assistant Professor, Department of Biological Science, Nicholls State University, Louisiana
- 2008-2010, Pradeep K. panuganti, MD, currently a resident in Texas Tech University of Health Sciences
- 2010, Daichi Maeda, MD, PhD, Assistant Professor, Department of Pathology, University of Tokyo, Japan
- 2010-2012, Stephanie Gaillard, Assistant Professor, Johns Hopkins University School of Medicine
- 2009-2012, Alex Stoeck, PhD, Research Scientist Leader, Merck Co.
- 2011-2012, Chen-Hsuan Wu, MD, Assistant Professor, Kaohsiung Chang Gung Memorial Hospital, and Chang Gung University college of medicine, Kaohsiung, Taiwan
- 2012-2013, Laura Ardighieri, MD, a fellow at the Anatomia Patologicaat Spedali Civili Brescia, Italy

- 2009-2013, Elisabetta Kuhn, MD, staff scientist, International Agency for Research on Cancer (IARC), Lyon, France
- 2007-2013, Bin Guan, PhD, NIDDK, NIH
- 2012-2014, Tae Mogami, MD, PhD, Department of Gynecology, Yokolohoma City University Medical Center, Japan
- 2013-2017, Yu Yu, PhD, Assistant Professor, University of Perth, Australia

Graduate and Undergraduate Students (Johns Hopkins University except Ms. Mahle)

- 2011-2015, Ren-Chin Wu, pathobiology graduate student (thesis student), currently an Associate Professor at the Chang-Gung University School of Medicine, Taiwan.
- 2008-2012, KaiLee Yap, pathobiology graduate student (thesis student), currently a postdoc fellow at the University of Chicago.
- 2010-2012, Min Gao, exchange/visiting graduate student from Shandong University/Zilu hospital, China.
- 2008-2010, Chen Xu, exchange/visiting graduate student from China Scholarship council, currently attending physician in the Department of Urology, the first affiliated hospital, Sun Yat Sen University, China
- 2005- 2009, Joon Park, pathobiology graduate student (thesis student), currently a Senior Scientist, Samsung Advanced Institution for Technology, Seoul, South Korea.
- 2009-2010, Elizabeth Chen, currently medical student in Uniformed Services University of Health Sciences, Bethesda, Maryland.
- 2007-2008, Vivek Murthy, currently a medical student at NYU.
- 2003-2005, Robert J. Oldt III, currently a medical student at UMDNJ, NY.
- 2005, Jim M. Yen, MD, currently a medical resident at the Medical Center of the University of South California, CA.
- 2005, Eric Cheng, currently a medical student at UMDNJ, NY.
- 2005, Ilena Neuberger, currently a medical student at UMDNJ, NY.
- 2007, Rebecca Bush, currently a medical student in Washington University School of Medicine, MO.
- 2007, David Chu, currently a medical student in University of Pittsburg, PA.
- 2007, Mandy Mahle, Queens University of Charlotte, NC, currently, a Gynecology Resident at the Johns Hopkins Hospital
- 2007-2009, Kevin Lee, currently a medical student in Albany Medical College, NY.
- 2007-2009, Paul Markowiski, previously lab assistant, currently a medical student in Robert Wood Johnson Medical School, NJ.
- Marilina Mascaró, visiting PhD student, Facultad de Farmacia Bioquimica, Catedra de Immunologia, Buenos Aires, Argentina
- 2010-2015, Ren-Chin Wu, PhD student, Pathobiology Graduate Program, Johns Hopkins University, Assistant Professor, Chang-Gung University, Taiwan

Ph.D. Student Qualification Committee:

- MD/PhD candidates in Cellular & Molecular Medicine Graduate Program:
  Saurubh Saha, Harith Rajagopalan, Chetan Bettego, Jordan Cummins
- PhD candidates in Cellular & Molecular Medicine Graduate Program:
  Ian Cheong, Carlo Rago and Jihye Yun
- Pharmacology Graduate Program:
  Xin Huang, Meng Li, Kibem Kim
- Pathobiology Graduate Program:
  Yin Yeh, Shaaretha Pelly, Sophie Lin Zhirong; Kah Suan Lim; Byung-Hak Kang, Shu- Han Yu

- Graduate Board Exam, Department of Chemical and Molecular Engineering, Johns Hopkins University:
  Serving as the Chair of the Exam committee for Melissa Thompson, CK Wang.

Ph.D. Student Thesis Committee:

- Melissa Thompson, PhD candidate, Department of Chemical and Molecular Engineering, Johns Hopkins University (Homewood campus), 2007- current
- Melissa Landek, PhD candidate, Pathobiology Graduate Program, Johns Hopkins Medical Institutions, 2008
- Hsin Chih Yeh, PhD candidate, Department of Bioengineering, Johns Hopkins University, 2008
- Christopher Puleo, PhD candidate, Department of Bioengineering, Johns Hopkins University, 2009
- Vasudev Bailey, PhD candidate, Department of Bioengineering, Johns Hopkins University, 2010
- Kelvin Liu, PhD candidate, Department of Bioengineering, Johns Hopkins University, 2011
- Yi Zhang, PhD candidate, Department of Bioengineering, Johns Hopkins University, 2013
- Chong-Guiy Wang, PhD candidate, Department of Health Policy, School of Public Health and Hygiene, 2015
- Young Yang, PhD candidate, Department of Health Policy, School of Public Health and Hygiene, 2018
- Kelly Kyker-Snowman, PhD candidate, Cell and Molecular Medicine Graduate Program, Johns Hopkins University, 2018

Participation in mentoring Gynecologic Pathology Fellows (*Johns Hopkins Hospital*):

- 2003 – 2005, Monica Srodon, M.D.
  Staff pathologist
  Greensboro Pathology Associates
  Greensboro, NC
- 2004 – 2006, Saeid Movahedi-Lankarani, M.D.
  Staff pathologist
  Hospital Pathology Associates
  St. Paul, MN
- 2006 – 2007, Dengfeng Cao, M.D., Ph.D.
  Assistant Professor
  Department of Pathology & Immunology
  Washington University School of Medicine
  St. Louis, MO
- 2006 – 2007, Kara Judson, M.D.
  Attending pathologist
  Lenox Hill Hospital
  New York, NY
- 2005 – Current, Anna Yemelyanova, M.D.
  (Current Fellow)
- 2007 – Current, Thomas McConnell, M.D.
  (Current Fellow)
- 2007 – 2008, Emanuela Veras, M.D.
  Memorial Sloan-Kettering Cancer Center

Awards Received by Dr. Shih's Trainees

- **JHU Pathology Young Investigator Day Research Award**, 2017, Yohan Suryo Rahmanto, PhD, research fellow
- **JHU Pathology Young Investigator Day Research Award**, 2017, Youngran Park, graduate student
- **1st place for basic science research for undergraduates,** 2016, University of Maryland at Baltimore County Dominique Munson, undergraduate student
- **Young Investigator Award in Basic Science, Department of Pathology, JHU,** 2016, Youngran Park, graduate student
- **HERA Research Award,** 2015**,** Yohan Suryo Rahmanto, PhD, research fellow
- **Collen's Dream Foundation for ovarian cancer research award,** 2014, Hiroyasu Kashima, MD, research fellow
- **Keio University School of Medicine Young Investigator Award, Japan,** 2014, Yusuke Kobayashi, research fellow
- **Young Investigator Award in Basic Science, Department of Pathology, JHU,** 2014, Fun Yuyu, postdoctoral fellow
- **Ovarian Cancer Research Foundation (OCRF) award, 2013,** Fun Yuyu, postdoctoral fellow
- **Oppo's Foundation for Ovarian Cancer Young Investigator Award,** 2013, Felix Zeppernick, research fellow
- **Scholar-in-Training Award, American Association for Cancer Research,** 2013**,** Ren-Chin Wu, graduate student
- **HERA Research Award,** 2013**,** Fnu Yuyu, PhD, research fellow
- **Collen's Dream Foundation for ovarian cancer research award,** 2013, Felix Zeppernick, MD, research fellow
- **YW Loke Award,** 2012, Yusuke Kobayashi, MD, PhD, research fellow, award from International Federation of Placenta Associations
- **HERA Research Award,** 2012**,** Elizabeth Kuhn, MD, research fellow
- **Scholar-in-Training Award, American Association for Cancer Research**, 2011, Kai-Lee Yap, graduate student
- **Ovarian Cancer Research Foundation (OCRF) Award**, 2011, Bin Guan, PhD, postdoctoral fellow
- **American Society of Clinical Oncology Young Investigator Research Grant,** 2011, Stephanie Gaillard, MD, PhD, research fellow
- **Scholar-in-Training Award by Aflac, Inc.,** 2011, Kai-Lee Yap, PhD graduate student
- **HERA Research Award,** 2011**,** Alex Stoeck, PhD, research fellow
- **Pathology Young Investigator Award,** 2011, Kai-Lee Yap, PhD graduate student
- **Pathology Young Investigator Award,** 2011, Elisabetta Kuhn, MD research fellow
- **Pathology Young Investigator Award,** 2011, Alex Stoeck, PhD research fellow
- **International Society of Gynecologic Pathology Fellowship Award,** 2011, Laura Ardigheri, research fellow, 2011
- **HERA Research Award,** 2010**,** Bin Guan, PhD, research fellow
- **UICC, ICRETT award**. 2010, Marilina Mascaró, visiting PhD student, Argentina
- **Pathology Young Investigator Award,** 2010, Kai-Lee Yap, PhD graduate student
- **HERA Research Award,** 2008**,** Stefanie Ueda, MD, research fellow
- **Pathology Department Young Investigator First Price Award in Basic Science,** 2008, Joon Park, Johns Hopkins Medical Institutions
- **HERA Research Award,** 2007**,** Natini Jinawath, MD, PhD, research fellow

- **Provost's undergraduate research award,** 2007, Chanont Vasoontara, Johns Hopkins University
- **Ovarian Cancer Research Fund (OCRF)**, 2006, Ritu Salani, MD, research fellow
- **Best Abstract Award,** 2006, Ritu Salani, MD, research fellow, International Gynecologic Cancer Society biannual meeting, Santa Monica
- **Provost's undergraduate research award**, 2006, Rebecca Busch, JHU undergraduate student
- **HERA Research Award,** 2005**,** Kentaro Nakayama, MD, PhD, research fellow
- **First Place Award for Research Fellow in Basic Research, Johns Hopkins Oncology,** 2005, Jim Sheu, PhD, research fellow
- **International Union Against Cancer Technology Transfer Fellowship,** 2004, Gudrum Pohl, MD, research fellow
- **HERA Research Award,** 2003**,** Brant Wang, MD, PhD, research fellow
- **Yong Investigator Award of the International Society of Gynecologic Pathologists**, 2004, Gad Singer, MD, research fellow
- **Howard Hughes Undergraduate Research Award**, 2003, Robert J. Oldt III, JHU undergraduate student
- **Provost's undergraduate research award**, 2002, Robert J. Oldt III, JHU undergraduate student

CLINICAL ACTIVITIES

Certification

- The American Board of Pathology --- Anatomic Pathology, 1997
- Medical Licensure: Maryland, 1997

Clinical Service Responsibilities (20% of total effort) at the Johns Hopkins Hospital

- **Attending Physician**- diagnostic pathology in routine gynecologic specimens
- **Consultant Pathologist**- gynecologic pathology, specifically gestational trophoblastic diseases (nationally and internationally)

ADMINISTRATIVE AND ORGANIZATIONAL ACTIVITIES

Administrative Appointments

- Co-director, the Breast and Ovarian Cancer Program, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Medical Institutions, 2014- current. Mainly involved in program development, research planning and educational activities.
- Planning Committee, the 7th Biennial Meeting of Asia-Pacific International Academy of Pathology, 2009-2011
- Johns Hopkins Oncology Center Tissue Core oversight committee, 2013-
- Johns Hopkins Professor Promotion Committee, 2013-
- Symposium organizer, Johns Hopkins Annual Ovarian Cancer Symposium, 2009- current.
- President of International Association of Chinese Pathologists, 2006-2007; received the *Excellent Service Award*, March 2, 2008
- President of North American Taiwanese Medical Association-Baltimore chapter, 2006-2008
- Faculty promotion committee, Department of Pathology, Johns Hopkins Medical Institutions, 2004

- PhD student qualification/thesis committees, 2002-current
- Pathology residency advisory committee, 2009-current

Editorial Board Appointments

- The American Journal of Pathology (2016-2019)
- Editor-in-Chief, Current Obstetrics and Gynecology Report (2012-2015)
- Cancer Research (2013-2015)
- The Journal of Pathology (2012-)
- Guest Editor, Journal of Oncology special issue in ovarian cancer targeted therapy, 2011
- International Journal of Gynecologic Pathology
- ISRN Pathology
- International Journal of Molecular Sciences (Molecular Pathology section)
- Journal of the Formosan Medical Association
- Frontiers in Women's Cancer

Journal Peer Review Activities

- Proceedings of National Academy of Science
- Cancer Research
- Clinical Cancer Research
- Oncogene
- Journal of Clinical Investigation
- Journal of Biological Chemistry
- International Journal of Cancer
- Gynecologic Oncology
- Cancer Letters
- Modern Pathology
- Placenta
- The American Journal of Pathology
- Laboratory Investigation
- Human Pathology
- The Journal of Obstetrics and Gynecology Research
- British Journal of Cancer
- International Journal of Gynecologic Pathology
- Gastroenterology
- Annals of Oncology
- American Journal of Obstetrics and Gynecology
- International Journal of Gynecologic Cancer

Professional Societies Membership

- American Association for Cancer Research, 2004-present
- American Society for Investigative Pathology, 2002-present
- International Association of Gynecologic Pathologists, 1998-present
- United States and Canadian Academy of Pathology, 1998-present
- International Society for the Study of Trophoblastic Disease, 2000-present
- Society for the Study of Reproduction, 2000-present
- American Medical Association, 1998
- International Federation of Placental Associations, 1996-present

Panelist in Study Sections and Grant Review Committees

- National Institute of Health, National Cancer Institute, member of Omnibus- Cancer Biology 1 study section, 2013
- National Institute of Health, National Cancer Institute, member of P50 SPORE study section, 2012-
- National Institute of Health, National Cancer Institute, , Ad Hoc member of Provocative Question study section, 2012
- National Institute of Health, National Cancer Institute, member of Cancer Molecular Pathobiology Study section (CAMP), 2006-2011 (*Recipient of "Brain Award" and "Humanitarian Award")
- National Institute of Health, National Cancer Institute, Ad Hoc member of R15 Academic Research Enhancement Award Study Section, 2011.
- National Institute of Health, National Cancer Institute, site visit adviser, EDRN Early Detection Network, Cancer Biomarkers Research Group, July 15, 2008
- National Institute of Health, National Cancer Institute, member of ZRG1 Onc-L (12)B Cancer Diagnostic & Treatment Study Section, March 2005, October 2005, March 2006, June 2006, February 2007 (member)
- The Wellcome Trust, London, United Kingdom, Research proposal reviewer, 1998 (Ad Hoc)
- National Institute of Health, National Cancer Institute, study section of IMAT, R21: "new innovative technology in cancer", 2002 (Ad Hoc)
- Israel Science Foundation (ISF), Research proposal reviewer, 2004 (Ad Hoc)
- US Department of Defense (USAMRMC/CDMRP) ovarian cancer research program, member of the review committee, April, 2005 (Ad Hoc)
- Cancer Research UK, April 2005, July 2008 (Ad Hoc)
- Netherlands Organization for Health Research and Development (ZonMw), Netherland, grant proposal reviewer for 80-007029-98-07041, March 2006 (Ad Hoc)
- Research Grants Council of Hong Kong, panel member and external reviewer, March 2006, December 2007
- US Department of Defense ovarian cancer research program-concept awards, member of the review committee, April, 2006 (Ad Hoc)
- Cancer Research UK, requested by the Translational Research in Clinical Trials Committee, July 2006 (Ad Hoc)
- U.S. Civilian Research Development Foundation, Arlington, Virginia, October 2006 (Ad Hoc)
- Swiss Nationals Science Foundation, Berne, Switzerland, January, 2007 (Ad Hoc)
- Kansas Masonic Foundation, Kansas Masonic Cancer Research Institute, 2007 (Ad Hoc)
- Invited reviewer requested by the Ministry of Science & Technology, Life Sciences Division, Israel, for Taiwanese Israeli scientific and technological cooperation, 2007
- Invited reviewer requested by the Sheffield Hospital Charitable Trust Medical Research Committee, UK, 2008
- Maryland Industrial Partnerships (MIPS) Program, University of Maryland College Park, 2008
- US Department of Defense (USAMRMC/CDMRP) ovarian cancer research program, member of the review committee, April, 2009 (Ad Hoc)
- American Institute of Biological Sciences (AIBS), May, 2010 (Ad Hoc)
- Calgary Laboratory Services Health Services Research Funding Competition, June, 2010 (Ad Hoc)
- National Medical Research Council, Singapore, January 2011.

Organizer, chair and moderator in conference organizations

- *Chair Moderator*, Poster Section In 4th Conference of the International Federation of Placenta Associations. Tokyo, Japan, 1998.
- *Symposium section chair,* Gestational trophoblastic disease. In XXVI International Congress of the International Academy of Pathology, Montreal, Canada, September 2006.
- *Moderator*, Pathobiology platform section, annual (the 97th) meeting of the United States and Canadian Academy of Pathology (USCAP), Denver, Colorado, March 2008.
- *Symposium organizer,* Ovarian Cancer Symposium- Elucidating Early Ovarian Carcinogenesis: Implications for Early Detection and Treatment. Sponsored by Department of Defense. Baltimore, Maryland, May 28-29, 2009.
- *Moderator,* Gynecologic Pathology platform section, annual (the 99th) meeting of the United States and Canadian Academy of Pathology (USCAP), Washington DC, March 2010.
- *Moderator,* Gynecologic Pathology platform section, annual (the 100th) meeting of the United States and Canadian Academy of Pathology (USCAP), San Antonio, TX, March 2011.
- *Section convener,* gynecologic pathology section, in the (scheduled) 7th Asia-Pacific International Academy of Pathology, Taipei, Taiwan, May 20-24, 2011.
- Chair of the Plenary Session 5: Prevention and Early Detection. In AACR Special Conference: Addressing critical questions in ovarian cancer research and treatment. Pittsburgh, Pennsylvania, October 3, 2017.

Advisory boards, committees and consultation groups

- **Scientific Advisory Committee,** Ovarian Cancer Research Foundation (OCRF), New York, 2013-
- **Oncology Tumor Specimen Core Oversight Committee**, Johns Hopkins Sidney Kimmel Cancer Center, 2013-
- **NCI Ovarian Task Force of Gynecologic Cancer Steering Committee,** 2012-2015
- **International Society of Gynecologic Pathology/World Health Organization (WHO) Nomenclature Committee for gynecological neoplasm**, 2012
- **External advisory board**, Ovarian Cancer SPORE at Fox Chase Cancer Center, 2013
- **International Society of Gynecologic Pathology Nomenclature Committee:** Gestational trophoblastic disease subcommittee, 2011-
- **Panelist** of an NIH sponsored consensus meeting for ovarian borderline tumor, Bethesda, 2003
- **Committee member** in the *National Academy for Clinical Biochemistry*-ovarian cancer marker Laboratory Medicine Practice Guidelines (tumor markers). 2003

Ad Hoc member in Award/Fellowship Committee

- Wittgenstein Award, funded by the Austrian Science Fund (FWF), 2007
- Moldovan Young Scientist Scholarship Program, United States Civilian Research & Development Foundation, 2007

RECOGNITION

Awards and Honors

- *The Best Intern Award,* McKay Memorial Hospital, Taiwan, 1988
- *TeLinde Research Award,* Division of Gynecologic Pathology, Department of Pathology, the Johns Hopkins Hospital, 1996-1998
- *Young Investigator Award,* The 13th Rochester Trophoblast Conference, Banff, Canada, 1996
- *Junior Achievement Award,* NIH/FDA Chinese American Association and Washington DC Chapter of Society of Chinese Bioscientists in America, 1998
- *Young Investigator Award,* International Society of Gynecological Pathologists, 2000.
- *Clinician Scientist Award,* Johns Hopkins University School of Medicine, 2002.
- *Election to hold the Endowed Chair* position as the 2nd Richard W. TeLinde Distinguished Professor, Johns Hopkins University School of Medicine, 2014.

Invited Talks and Panels

- *Invited Speaker*, "Pathology of benign and malignant lesions of intermediate trophoblast". In 4th Conference of the International Federation of Placental Associations. Tokyo, Japan, 1998.
- *Invited Speaker* "Molecular surrogates of tumor progression in body fluids". Bowling Green State University, Ohio, 2001.
- *Invited Speaker,* "Molecular Landscape of Ovarian cancer and its implication for early diagnosis". Chang-Gung Memorial Hospital, Taiwan, 2002.
- *Invited Speaker,* "Gestational trophoblastic diseases", Taipei Medical University, Taiwan, 2002.
- *Invited Speaker,* "Molecular Landscape of Ovarian cancer". National Cancer Institute/NIH, 2002.
- *Invited Lecturer,* "Gestational trophoblastic diseases", Pathology Laboratory, National Cancer Institute/NIH, 2002.
- *Invited Speaker,* "Circulating tumor-released DNA as the marker for early detection of cancer". Pathology Grand Round, MD Anderson Cancer Center, January 2003.
- *Invited Lecturer,* "Pathology of gestational trophoblastic diseases", MD Anderson Cancer Center, January 2003.
- *Invited Speaker, "*Digital PCR and clinical applications". At the 11th annual meeting of "Nuclei acid-based technologies" Baltimore, June 2003.
- *Invited Speaker, "*New technologies in exploring disorders of human implantation and trophoblast". Perinatology research branch, NICHD, Detroit, May, 2003.
- *Invited Speaker, "*Pathology of intermediate trophoblastic lesions". NICHD, Detroit, May, 2003.
- *Invited Speaker, "*Allelic imbalance in detecting ovarian and other types of cancer". At the 4th Principal Investigator Meeting of "Innovative Molecular Analysis Technologies (IMAT) Program" sponsored by NIH. San Diego, June 2003.
- *Invited Speaker, "*Molecular Genetic Markers for Cancer Detection in Blood". At the Cambridge Healthtech Institute's 11th Annual Molecular Medicine Tri-Conference, San Francisco, March 2004.
- *Invited Speaker,* "Molecular pathways of ovarian cancer-translational cancer research by analyzing cancer genome". Division of epidemiology and genetics, NCI/NIH, Rockville, Maryland, September 16, 2004.

- *Invited Speaker,* "DNA preparation for cancer genomic study-the pathologist's views". Lecture in the G.O.T. (Getting Optimal Targets) summit series, Genomic and Proteomic Sample Preparation, Boston, May 3-4, 2005.
- *Invited Speaker,* "Identification of novel genes for cancer therapy and diagnosis by exploring cancer genome". 10th Annual Meeting of Chinese Biopharmaceutical Association, Rockville, Maryland, June 18, 2005.
- *Guest Speaker,* "Exploring ovarian cancer genome- new insights and old challenges". Fox Chase Cancer Center, Philadelphia, Pennsylvania, August 9, 2005.
- *Invited Speaker,* "Relationship of serous borderline tumor and carcinoma". The annual companion meeting of the International Association for Gynecologic Pathologists. Atlanta, Georgia, Feb. 12, 2006.
- *Invited Speaker,* "Identification of novel molecular targets for ovarian cancer therapy". University of Oslo. Olso, Norway, Feb. 27, 2006.
- *Invited Speaker,* "Translating Ovarian Cancer Genome- New Genes for Prognostic Prediction and Targeted Therapy". Pathology Grand Round, University of British Columbia, Vancouver, Canada, March 13, 2006.
- *Invited Speaker,* "Trophoblastic tumors and tumor-like lesions". Department of Pathology, Vancouver Hospital, Canada, March 13, 2006.
- *Invited Speaker, "Gestational trophoblastic tumor-an intellectual Odyssey".* Second Investigative Pathology Conference, Cleveland Clinics, Cleveland, Ohio, June 3, 2006
- *Invited Speaker,* "Applications of HLA-G expression in the diagnosis of human neoplastic diseases". Forth International conference on HLA-G, Paris, France, July 12, 2006.
- *Invited Speaker,* "Trophoblastic tumors- molecular classification and pathogenesis". Biennial Meeting of International Gynecological Cancer Society, Santa Monica, October 17, 2006.
- *Invited Speaker,* "Analyzing ovarian cancer genome- from gene discovery to therapeutic targets". Sloan Kettering Memorial Hospital, New York, December 11, 2006.
- *Distinguished Visiting Professor*, "Ovarian cancer- molecular pathways, diagnostic markers and therapeutic targets". Pathology Grand Round, Emory University, March 9, 2007.
- *Distinguished Visiting Professor*, "New concept in ovarian cancer- the dualistic pathway and its implications". Pathology Grand Round, Yale University School of Medicine, April 19, 2007.
- *Invited Speaker,* "Translational Research and New Diagnosis in Ovarian Cancer". The 12th Taiwan Joint Cancer Conference (Gynecologic Oncology section), Taipei, Taiwan, May 5, 2007.
- *Invited Speaker,* "Genomic analysis of ovarian cancer from marker discovery to translational applications". Taipei Medical University, Taipei, Taiwan, May 3, 2007.
- *Invited Speaker,* "Analyzing Ovarian Cancer Genome for Marker Discovery". International Symposium on Biomarkers Discovery in Human Cancers, Tainan, Taiwan, May 7, 2007.
- *Invited Speaker,* "Analyzing ovarian cancer genome for therapeutic target discovery". 12th annual meeting of SCBA, University of Maryland Shady Groove Conference Center, MD, June 2, 2007.
- *Invited Speaker,* "Update in gestational trophoblastic disease". Surgical Pathology Update, Leipzig, Germany, June 15, 2007.
- *Invited Speaker,* "The roles of NAC-1 in chemoresistance in ovarian carcinoma". The Montebello Conference, Norway, June 18, 2007.
- *Invited Speaker,* "Exploring ovarian cancer genome- from marker discovery to therapeutic targeting". Symposium of Toronto Ovarian Cancer Research Network/University of Toronto Health Network, Toronto, Canada, November 2, 2007.
- *Invited Speaker,* "Biological and clinical significance of Rsf-1 gene amplification in ovarian cancer". Grand Round at the Cancer Institute of New Jersey, April 2, 2008.

- *Invited Speaker,* "Analyzing cancer genome to identify new cancer-associated genes in ovarian cancer". In the series of Molecular Pathology seminar, University of Maryland at Baltimore, Baltimore, April 11, 2008.
- *Invited Speaker,* "Molecular etiology of drug resistance in ovarian cancer". Symposium on Ovarian Cancer Research, Medical University of South Carolina, Charleston, South Carolina, May 2, 2008.
- *Invited Speaker,* "Identifying new cancer genes through analyzing cancer genomics- Rsf-1 amplification in ovarian cancer". National Health Research Institution, Taiwan, August 5, 2008.
- *Invited Speaker,* "Early detection and treatment of ovarian cancer: shifting from early stage to minimal volume of disease based on a new model of carcinogenesis". 7th Biennial Ovarian Cancer Symposium, Marsha Rivkin Center for Ovarian Cancer Research, Charleston, Seattle, Washington, September 4-5, 2008
- *Invited Speaker,* "Functional genomic analysis of ovarian cancer", in honor of Dr. Meenhard Herlyn's achievement in cancer research, The Wistar Institute, Philadelphia, PA, August 10, 2009
- *Invited Speaker,* "Notch3 signaling in ovarian cancer", Institute of Genomic Medicine, China Medical University, Taiwan, August 21, 2009
- *Invited Speaker*, "Targeted therapy in ovarian cancer", Ovarian Cancer SPORE meeting, Fox Chase Cancer Center, Philadelphia, PA, September 26, 2009
- *Invited Speaker,* 7th International Seminar at Lake Hamana- Surgical and Molecular Pathology of the Endometrium, Placenta, and Ovary. "Pathology of gestational trophoblastic diseases", and "Molecular pathogenesis of ovarian cancer", Hamamatsu, Shizuoka, Japan, November 7, 8, 2009
- *Invited Speaker*, "Gestational trophoblastic diseases", Grand Round in the Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY, December 7, 2009
- *Invited Speaker*, "The origin and pathogenesis of epithelial ovarian cancer- a proposed unifying theory", Grand Round, Department of Gynecologic Oncology, MD Anderson Cancer Center, Houston, TX, February 1, 2010
- *Invited Speaker*, "Definition and characterization of low-grade and high-grade ovarian serous carcinomas", 2nd Annual European Gynecologic Oncology Congress, Athens, Greece, February 12-13, 2010
- *Invited Speaker*, "Clear cell carcinoma of the ovary", Gynecologic Pathology Specialty Conference, United States & Canadian Academy of Pathology, 99th annual meeting. Washington DC, March 20-26, 2010
- *Invited Speaker*, "Molecular pathology of ovarian clear cell carcinoma", University of British Columbia, Vancouver, Canada, June 24, 2010
- *Invited Speaker*, "The origin and pathogenesis of epithelial ovarian cancer- a proposed unifying theory", Fox Chase Cancer Center, Philadelphia, July 15, 2010
- *Invited Speaker*, "The origin and pathogenesis of epithelial ovarian cancer- a proposed unifying theory", Department of Pathology, Chang-Gang Memorial Hospital at Kaohsiung, Taiwan, August 12, 2010
- *Invited Speaker*, "The biological roles of NAC1 in cancer pathogenesis", Department of Developmental Biology and Regeneration Medicine, Mount Sinai School of Medicine, New York City, New York, September 2, 2010
- *Invited Speaker*, "Chromatin remodeling in ovarian cancer", Department of Molecular and Cellular Biology, Rutgers University, New Jersey, January 11, 2011
- *Invited Speaker*, "Genomic analysis of gynecological cancer", National Cancer Research Center, Tokyo, Japan, June 30, 2011

- *Invited Keynote Speaker*, "Ovarian cancer is an imported disease- fiction or fact", The 10th annual meeting of targeted therapy in gynecologic oncology, Izumo, Shimane, Japan, July 2, 2011
- *Invited Keynote Speaker*, "Pathogenesis of ovarian clear cell carcinoma", The 10th annual meeting of targeted therapy in gynecologic oncology, Izumo, Shimane, Japan, July 2, 2011
- *Invited Speaker*, "Diagnosis of biological implication of serous tubal intraepithelial carcinoma", Chang-Kung Memorial Hospital, Kaohsiung, Taiwan, July 6, 2011
- *Invited Speaker*, "Ovarian cancer genetics- latest insight", The Boehringer Ingelheim Conversations in Oncology, Vienna, Austria, October 28-29, 2011
- *Invited Speaker*, "Integrated molecular analysis of ovarian cancer", Virginia Polytechnic Institute and State University, Arlington, Virginia, February 22, 2012.
- *Invited Speaker,* "Intertumoral heterogeneity- how many types of cancers do my patients have?" In the symposium of "Intratumoral and intertumoral heterogeneity in ovarian cancer", American Association for Cancer Research (AACR) annual meeting, Chicago, April 2, 2012
- *Invited Speaker*, "Genomic landscape in gynecologic cancer and its biological and translation implications", Department of Pathology and Laboratory Medicine, University of California at Irvine, April 16, 2012.
- *Lecture,* "Molecular analysis of serous tubal intraepithelial carcinoma", the 3rd Johns Hopkins Ovarian Cancer Symposium, Baltimore, Maryland, May 18, 2012.
- *Invited Keynote Speaker*, "Endometriosis-related ovarian cancer", The 16th Korea-Japan, the 2nd Korea-Taiwan-Japan Joint Conference for Gynecological Pathology, Kumamoto University, Kumamoto City, Japan, May 26, 2012.
- *Invited Speaker*, "Genomic landscape in gynecologic cancer- a road map to new therapeutics", Bristol-Myers Squibb Lectureship, Kumamoto City, Japan, May 27, 2012.
- *Invited Speaker*, "Genomic landscape in gynecologic cancer- a road map to new therapeutics", Kyoto University, Kyoto, Japan, May 29, 2012.
- *Invited Keynote Speaker*, "Genomic analysis of gynecological cancer and their clinical implications", In annual meeting of Korean Division of International Association of Pathologists, Seoul, South Korea, October 18, 2012.
- *Invited Speaker*, "The tumor suppressor role of ARID1A in human cancer", Kyung Hee University, Seoul, South Korea, October 18, 2012.
- *Invited Speaker*, "The tumor suppressor role of ARID1A in human cancer", Korean National Cancer Center, Seoul, South Korea, October 19, 2012.
- *Invited Speaker*, "The origin of ovarian cancer- clear cell carcinoma", International Society of Gynecologic Pathologists companion meeting of United States and Canadian Association of Pathology annual meeting, Baltimore, Maryland, March 3, 2013.
- *Invited Speaker*, "Genomic landscape of ovarian cancer and its translational implications", The Wistar Institute, Philadelphia, April 15, 2013.
- *Invited Speaker*, "Molecular alterations in serous tubal intraepithelial carcinoma", 4th Ovarian Cancer Symposium, the Memorial Sloan Kettering Cancer Center, New York, May 15, 2013.
- *Invited Speaker,* "Emerging therapeutics in gynecologic cancer", China Medical University, Taichung, Taiwan, July 7, 2013
- *Invited Speaker,* "Bokhman's dualistic model of endometrial carcinoma- revisited", Chang-Kung Memorial Hospital, Kaohsiung, Taiwan, July 8, 2013
- *Invited Speaker*, "Genomic analysis and pathogenesis of uterine carcinoma", Taipei Veterans General Hospital, Taipei, Taiwan, July 11, 2013.
- *Invited Speaker*, "The Genomic landscape and origin of ovarian cancer", The 18th Taiwan Joint Cancer conference, Taipei, Taiwan, July 13, 2013.

- *Invited Lecturer*, "The origin and pathogenesis of ovarian cancer", The 2013 International Diagnostic Pathology Course, Tokyo, Japan, July 14, 2013.
- *Invited Speaker,* "Ovarian cancer is an imported disease- fiction or fact?" Charite Hospital (Mitt campus), Berlin, Germany, September 11, 2013
- *Invited Lecturer,* "Various topics in gynecologic pathology and oncology", Nederland Master Class in ovarian cancer. Berlin, Germany, September 12, 2013
- *Invited Lecturer,* "Understanding the molecular mechanisms in the development of chemoresistance in cancer", Rush University Medical Center, Chicago, October 30, 2013
- *Invited Speaker*, "Ovarian cancer is an imported disease – translational implication and beyond", Ovarian Cancer SPORE meeting, MD Anderson Cancer Center, Houston, TX, May 28, 2014
- *Invited Speaker,* "The cell of origin of ovarian high-grade serous carcinoma". Tzu-Chi Hospital, Hui-Lien, Taiwan, June 20, 2014
- *Invited Speaker,* "Molecular pathogenesis of high-grade serous carcinoma". Symposium of the semiannual National Gynecologic Oncology Group (GOG, now NGR) meeting. Symposium title: "New paradigms in the pathogenesis of high-grade serous carcinoma: translating biological advances into prevention". Chicago, IL. July 9, 2014
- *Invited Speaker: "ARID1A, a new tumor suppressor, in Type I ovarian cancer"* In 2014 5th Ovarian Cancer Symposium, Toronto, Canada. September 22, 2014.
- *Invited Speaker, "*The origin and molecular biology of ovarian cancer: the role of fallopian tube". In 2014 Gynecologic Cancer Survivors Course, Baltimore, MD, September 27, 2014.
- *Grand Round Speaker, "*Chromatin remodeling and tumor suppression- a cross talk of genetics and epigenetics" Pathology Grand Round, Johns Hopkins Medical Institutions, October 20, 2014.
- *Invited Special Lecturer, "*New paradigm in the origin of ovarian carcinoma- from molecular to clinical implications". The 128th Meeting of the Kanto Society of Obstetrics and Gynecology, Matsumoto City, Nagano, Japan, October 25-26, 2014.
- *Invited Special Lecturer, "*The biology of ARID1A, a chromatin remodeling gene, in tumor suppression". National Sun Yat Sen University, Kaohsiung City, Taiwan. October 28, 2014.
- *Invited Speaker,* Talk-1 "Molecular prognostic factors: Will it affect treatment decision?" Talk-2 "Genetic innovations in screening for ovarian cancer" Talk-3 "Pathology evaluation of gestational trophoblastic neoplasia", Turkish GOG Congress, Antalya, Turkey. November 20-22, 2014.
- *Invited Speaker, "*Molecular etiology and pathogenesis of ovarian cancer". In 2014 Ella T. Grasso Memorial Conference New Haven, CT, December 3, 2014.
- *Invited Speaker, "*Molecular innovations for early detection of gynecologic cancer using cervical cytology specimens". 2015 Conference of Chinese Society of Colposcopy and Cervical Pathology. Beijing, China, May 22-24, 2015.
- *Invited Speaker*, "Molecular Classification of Ovarian Cancer". Qilu Hospital of Shandong University. China, May 26, 2015.
- Invited Speaker, "Translational Implications of Genomic Analysis in Gynecologic Cancer". CGMH-Kaoushiang, Taiwan, May 16, 2015.
- Invited Speaker, topic 1: "Intermediate trophoblastic tumors and tumor-like lesions" topic 2: "The dualistic model of ovarian carcinogenesis, revisited, revised and expanded" In Professor TY Chen Memorial Symposium, Taipei Medical University, Taipei, Taiwan, June 27, 2015.
- Invited Seminar Speaker, "Targeting SYK as a new strategy to sensitize paclitaxel in ovarian cancer". Massachusetts General Hospital (Center for Cancer Research) and Harvard Medical School, Boston, Massachusetts. September 2, 2015.

- Invited Speaker, AACR special meeting- “Endometriosis-associated Ovarian Cancer“. Advances in Ovarian Cancer Research: Exploiting Vulnerabilities. Orland, Florida. October 19, 2015.
- Grand Round Speaker, “The cell of origin of ovarian cancer- a paradigm shift and clinical implications” Karmanos Cancer Institute, Detroit, MI, March 24, 2016
- Invited Speaker, “Personalized medicine in gynecologic cancer- the challenges and promise” In Taiwan Join Cancer Conference, May 15, 2016.
- Invited Speaker, “The promise of translational gynecologic research at the post-genomic era” Veteran General Hospital- Taipei, Taiwan, May 16, 2016
- Invited Speaker, “Molecular Genetic Landscape of Endometriosis- a time to re-define what is cancer?”, in Asia-Pacific Society of Molecular Immunohistology, December 11, 2016, Taipei, Taiwan.
- Invited Speaker, “Molecular Genetic Landscape of Endometriosis” First Congress of Taiwan Endometriosis Society, December 17, 2016.
- Invited Distinguished Grand Round Speaker, “Molecular Genetic Landscape of Endometriosis” Thomas Jefferson University, Philadelphia, January 4, 2017.
- Invited Speaker, “Early detection of ovarian cancer in BRCA1/2 carriers”, the annual Basser Symposium for BRCA research. Philadelphia, May 4, 2017.
- Invited Speaker and Visiting Lecturer, “Various topics of Gynecologic Pathology”, Mongolian National University Medical School, Ulaanbaatar, Mongolia, June 19- 22, 2017.
- Invited Speaker, “The Pathology of Human Suffering”, in Professor Huang Memorial Lecture of Pathology, Taipei Medical University, Taipei, Taiwan, June 28, 2017.
- Invited Speaker, “Molecular etiology in ovarian clear cell and low-grade serous carcinomas”, NRG Oncology Semi-Annual Meeting, Philadelphia, Pennsylvania, July 13, 2017.
- Invited Speaker, “Molecular diagnostics of ovarian cancer using cervical-vaginal fluid”, in NIH/NCI EDRN meeting. Seattle, Washington, September 12, 2017.
- Invited Speaker, “PapGene and PapDREAMing for early detection of ovarian cancer”, AACR Special Conference: Addressing critical questions in ovarian cancer research and treatment. Pittsburgh, Pennsylvania, October 3, 2017.
- Invited Speaker, “Somatic mutations in ovarian cancer precursors including STIC in the absence of carcinoma.” At 6th US Department of Defense Ovarian Cancer Research Program Ovarian Cancer Consortium Mini-symposium, New York University Medical Center, New York City, October 27, 2017.
- Invited Speaker, “Cancer Implications for Patients with Endometriosis”, in the symposium of “Breast, Ovary & Endometriosis: Investigating the role of sex hormones in the etiology and treatment”. New York City, October 28, 2017.
- SKCCC Translational Cancer Seminar, “Translational implications of analyzing mutation landscape in gynecologic cancer precursors”, Department of Oncology, Johns Hopkins Medical Institutions, November 9, 2017
- Grand Round Speaker, “Endometriosis- New Biology and Questions”, Department of Gynecology, Greater Baltimore Medical Center, Baltimore, Maryland, November 17, 2017
- Invited Speaker, “Cancer-driver mutations in endometriosis“. American Association of Gynecologic Laparoscopists (AAGL)-Beijing meeting, Beijing, China, December 9, 2017.
- Invited Speaker, “The Origin of Endometriosis- new insights into an old question”, Taiwan Endometriosis Society (TES) 2017 Annual Meeting, December 10, 2017.
- Grand Round Speaker, “Endometriosis-related ovarian neoplasms” Memorial Sloan Kettering Comprehensive Cancer Center Gynecologic Oncology, New York City, February 8, 2018.

- Emerging Frontiers in Biomedical Research Seminar Series, “Molecular landscape in endometriosis”. RWJMS Basic Science Departments, Rutgers University/Robert Wood Johnson Medical School, Piscataway, New Jersey, March 20, 2018.
- Translational Medicine Institute, “Translational medicine- the time is now”. Taipei Medical University, April 17, 2018.
- The Tina Brozman Ovarian Cancer Research Consortium Symposium, “Integration of advanced genomic and bioengineering approaches for early detection and prevention of ovarian cancer” and “Applying DREAMing to detect epigenetic markers in ovarian cancer”. New York City, May 7, 2018.
- AAGL International Conference. “Clonal origin of adenomyosis and endometriosis” Beijing, China, September 12-16, 2018.
- Invited Speaker, “The stem cell theory of endometriosis”, Taiwan Endometriosis Society (TES) 2018 Annual Meeting, Taipei, Taiwan, November 10, 2018.
- “The origin of ovarian cancer precursor species”, at Tzu Chi University, Hualien, Taiwan, January 24, 2019.
- Invited Speaker, “Pathology and pathogenesis of ovarian low-grade serous carcinoma” Low-grade ovarian cancer symposium, Miami, Jan 31, 2019
- Invited Speaker, “Inflammation in endometriosis- what we can learn from cancer biology?” Annual meeting of Endometriosis Foundation USA, New York City, New York, March 8, 2019.
- Invited Speaker, Mini-symposium on endometriosis of SRI meeting. “Somatic mutations and evolution of endometriosis species.” Paris, France. March 15, 2019.

OTHER NONPROFESSIONAL ACTIVITIES

Photography website: http://www.shih-photography.com

EXHIBIT B

Fed. R. Civ. P. 26(a)(2)(B)(v) Disclosure for Dr. Ie-Ming Shih, M.D.

Deposition Date: July 11, 2017

Richardson, et al. v. C.R. Bard, Inc., No. 2:13-ev-20036 (S.D. W. Va.)

Barker, et al. v. C.R. Bard, Inc., No. 2:13-ev-33690 (S.D. W. Va.)

Cuffee, et al. v. C.R. Bard, Inc., No. 2:14-ev-02528 (S.D. W. Va.)

Cooley, et al. v. C.R. Bard, Inc., No. 2:14-ev-07543 (S.D. W. Va.)

Deposition Date: May 10, 2018

Rhonda Meredith vs. Larry Mapow (N.J. Super. Ct.)

Deposition Date: October 4, 2018

Jacobsen v. Ethicon, Inc., No. 2:13-cv-24530 (S.D. W. Va.)

Kmiec v. Ethicon, Inc., No. 2:13-cv-24531 (S.D. W. Va.)

Murray v. Ethicon, Inc., No. 2:13-cv-24573 (S.D. W. Va.)

Rapacki v. Ethicon, Inc., No. 2:13-cv-19758 (S.D. W. Va.)

Deposition Date: October 5, 2018

Repka v. Ethicon, Inc., No. 2:13-cv-26198 (S.D. W. Va.)

Siegrist v. Ethicon, Inc., No. 2:14-cv-17889 (S.D. W. Va.)

Hudspeth v. Ethicon, Inc., No. 2:15-cv-04163 (S.D. W. Va.)

Townson v. Ethicon, Inc., No. 2:13-cv-12954 (S.D. W. Va.)